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Review article

Immunobiologic treatment for Chronic Rhinossinusitis: sistematic review

Tratamento com imunobiológicos na rinossinusite crônica:revisão sistemática

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Abstract

Objective: To conduct a systematic review on the use of immunobiologics in the treatment of patients with chronic rhinosinusitis (CRS).**Materials and Methods:** This is a systematic review that meticulously analyzed 10 publications from the last 5 years (2018-2023) that discussed the use of immunobiologics in the treatment of chronic rhinosinusitis. The databases used were Pubmed and BVS (Virtual Health Library), with inclusion criteria being clinical trials and randomized clinical trials, and excluding studies that did not address the theme. The Jadad Scale and the NEWCASTLE – OTTAWA Quality Assessment Scale were used as tools for analyzing the studies.**Results:** Ten articles were analyzed, including clinical trials, observational studies, and cohort studies, all dated within the last five years. It was demonstrated that immunobiologics (such as Benralizumab, Omalizumab, Reslizumab, Dupilumab, and others) are capable of reducing CRS symptoms – such as rhinorrhea and nasal congestion – and comorbidities like asthma, in addition to improving the quality of life of the monitored patients who received treatment during the evaluation period.**Conclusion:** The treatment with the immunobiologics evaluated in this systematic review showed clinical, laboratory, and endoscopic superiority compared to placebo. Additionally, they demonstrated good safety, tolerability, and few adverse effects.
Keywords: Chronic Rhinosinusitis. Monoclonal Antibody. Pharmacological Treatment. Systematic Review. Asthma.

Resumo

Objetivo: realizar uma revisão sistemática sobre o uso de imunobiológicos no tratamento de pacientes portadores de rinossinusite crônica. **Materiais e Métodos:** trata-se de uma revisão sistemática que analisou criteriosamente 10 publicações, datadas dos últimos 5 anos (2018-2023), que abordaram o uso de imunobiológicos no tratamento da rinossinusite crônica. Foram utilizadas, como base de dados Pubmed e BVS (Biblioteca Virtual em Saúde), tendo como critérios de inclusão ensaios clínicos e ensaios clínicos randomizado. Foram excluídos da análise os estudos que não abordavam a temática. Como ferramenta de análise dos trabalhos, foram utilizadasa Escala Jadad e a Escala de Avaliação de Qualidade NEWCASTLE – OTTAWA. **Resultados:**foram analisados dez artigos, entre ensaios clínicos, estudos observacionais e estudos de coorte. Demonstrou-se que imunobiológicos (como Benralizumabe, Omalizumabe, Reslizumabe, Dupilumabe e outros) são capazes de reduzir sintomas de rinossinusite – como rinorreia e congestão nasal – e comorbidades, como asma, além de melhorar a qualidade de vida dos pacientes monitorados e que receberam tratamento durante o período de avaliação. **Conclusão:** o tratamento com os imunobiológicos avaliados nesta revisão sistemática mostrou superioridade clínica, laboratorial e endoscópica em relação ao placebo. Além disso, mostraram boa segurança, tolerabilidade e poucos efeitos adversos.
Palavras-chave: Rinossinusite Crônica. Anticorpo monoclonal. Tratamento medicamentoso. Revisão Sistemática. Asma.

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Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disease of the upper airway and paranasal sinuses, which generates economic impacts and quality of life for patients, being common recurrent disease and even chronic conditions[1].

CRS is usually more prevalent in places with high levels of humidity, lower socioeconomic status - or places with high social inequality – as well as places with poor hygiene – where the allergic profile of CRS may be more common. It is estimated that about 4% of the population of industrialized/industrializing countries are diagnosed with CRS[2] and, of this, about 2/3 may have asthma as a comorbidity[1,2].

In the United States, CRS is estimated to affect about 11% of the adult population, becoming one of the most common chronic conditions. It is believed that the prevalence of this disease is high due to factors such as environmental pollution, smoking and allergies. In Europe, the prevalence of CRS varies between 10% and 15% of the population, depending on the country and environmental and socioeconomic conditions. Among the factors contributing to these numbers on this continent are air pollution and high humidity levels. In Brazil, it is estimated that the prevalence of CRS ranges from 5% to 12% of the population, with regional variations influenced by climatic and socioeconomic factors. Regions with high levels of humidity and pollution, such as densely populated urban areas, have higher CRS rates[2-5].

Among the most commonly identified symptoms and signs, CRS leads to nasal congestion, rhinorrhea, postnasal drip, facialgia (or feeling of pressure in the face)[1,2]. In addition, CRS can be divided into CRSwNP (chronic rhinosinusitis with nasal polyps) and CRSw/oNP (chronic rhinosinusitis without nasal polyps)[3]. Among these, the CRSwNP is marked by the Th2 profile immune response, which involves the production of cytokines, eosinophils and IgE[6]. In addition, CRSwNP is often associated with several comorbidities, such as Asthma, Allergic Rhinitis[5]and Aspirin-Exacerbated Respiratory Disease (AERD)[2].

Usually, cases of CRS are treated with nasal/systemic corticosteroids, in addition to nasal lavage with saline solution, antibiotics or even endoscopic nasal surgeries, aiming at the control of the disease[6]. Treatment using immunobiologics, which are monoclonal antibodies, aims to combat the intrinsic actions of the interleukins involved in the inflammatory process (such as IL-2, IL-4, IL-5, IL-13 and IgE)[2], so that each immunobiological is specific for a group of cytokines.

This systematic review is based on the need to consolidate evidence about the effectiveness of immunobiologics in the treatment of chronic rhinosinusitis (CRS), a condition that significantly affects the quality of life of patients and is often associated with comorbidities such as asthma and

allergic rhinitis. Given the recent introduction of immunobiologics as therapeutic options, it is crucial to rigorously evaluate clinical, endoscopic and quality-of-life outcomes in comparison to conventional treatments. This review aims to fill a knowledge gap by analyzing recent and relevant studies, providing robust data that can guide clinical practice and improve CRS management.

Therefore, the objective was to carry out a systematic review on the effectiveness of treatment of patients with chronic rhinosinusitis using immunobiologics.

Materials and Methods

This is a systematic review, which is based on the search and careful analysis of published studies. The question that guided the investigation was "What are the results of treatment of patients with chronic rhinosinusitis using immunobiologics?".

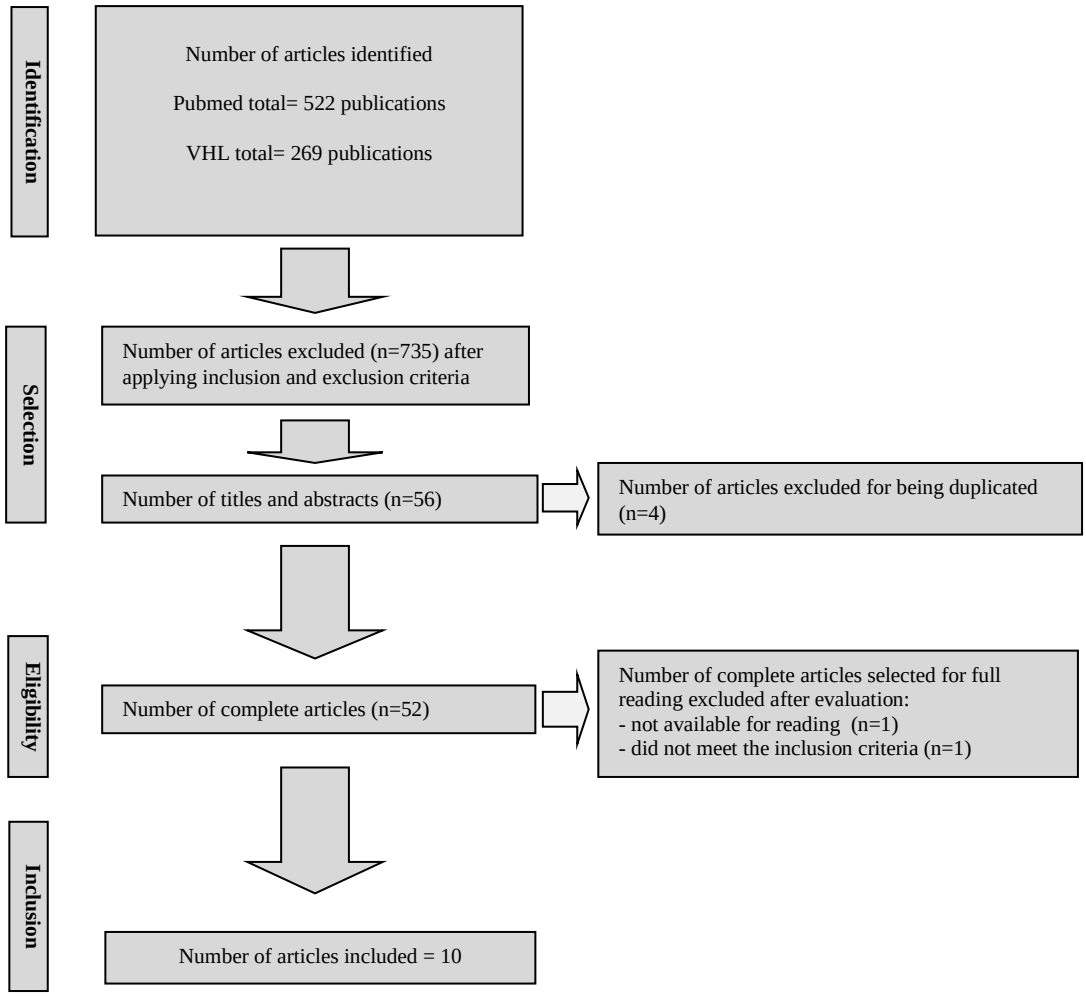
The studied population consisted of patients with CRS aged over 18 years, with and without nasal polyps and having comorbidities such as asthma, Aspirin-Exacerbated Respiratory Disease (AERD) or Allergic Rhinitis. The clinical intervention evaluated in the studies was the use of immunobiological medication for the treatment of patients with CRS. The accepted control group was composed of patients who did not use immunobiological for CRS treatment. The results investigated were the improvement of signs/symptoms of nasal congestion, hypo/anosmia, rhinorrhea, as well as improvement in endoscopic evaluation – of patients with CRSwNP.

To obtain the review works, the Virtual Health Library and PUBMED were used as databases. The languages used to identify articles in these two databases were Portuguese, English and Spanish. The search was carried out on 11/08/2023 using the following descriptors: "sinusitis", "treatment" "biologics" and "polyps", in Spanish, respectively, "*sinusitis*", "*tratamiento*", "*biológicos*" and "*pólipos*" and in Portuguese, "*sinusite*", "*tratamento*", "*biológicos*" and "*pólipos*".

The inclusion criteria were: clinical trials, randomized clinical trials, publication in the last five years. The exclusion criteria considered were: studies not available in full, studies involving Chinese medicine, systematic reviews, studies involving treatment with traditional Chinese medicine and treatment with procalcitonin and/or amphotericin-B.

The process of identification of articles in the two databases was carried out on 08/11/2023.

Figure 1. Flowchart of the article screening process for review.



After the insertion of descriptors in the database of the Virtual Health Library, 269 works were identified. At the end of the application of the exclusion criteria by reading the titles and abstracts, only 29 publications were selected for full reading.

After the insertion of descriptors in the PUBMED database, 522 publications were identified. After applying the exclusion criteria by reading the titles and abstracts, only 27 articles were selected for full reading (Figura 1).

During the selection process, after reading the articles identified in the two databases, 4 duplicate jobs were removed. In the eligibility phase, the selected articles were carefully analyzed taking into account title, year of publication, authors, place of publication, immunobiologic involved in the studies, as well as the objectives and main results. At this selection stage, 1 article was removed because it was not available for full reading and 41 because they did not adequately meet the aforementioned inclusion and exclusion criteria. After the entire process of evaluating the papers chosen for full reading, only 10 articles were included in the systematic review.

To evaluate the quality of the selected papers, the Jadad scale was used for the evaluation of randomized studies and the Newcastle Ottawa scale for the evaluation of the cohort study (Chart 1 and Chart 2).

In the presence of divergence in the selection process of a particular article for systematic review, the author MJSM was responsible for resolving the doubt.

Chart 1. Jadad Scale: Tool used to assess the quality of randomized trials.

Author	1a. Randomization	1b. Appropriate Concealment	1c. Inappropriate Concealment	2nd. Double Blind	2b. Appropriate	2c. Inappropriate	Detailing	**Total Score**
Jonstam, K. *et al*., 2018	1	0	0	1	0	0	0	**2/5**
Bachert, C. *et al*., 2019	1	0	0	1	0	0	0	**2/5**
Bachert C. *et al., 2019*	1	1	0	1	1	0	1	**5/5**
Bachert, C. *et al*., 2020	1	0	0	1	0	0	1	**3/5**
Fujieda, S. *et al*., 2021	1	0	0	1	0	0	0	**2/5**
Bachert C. *et al., 2021*	1	0	0	1	0	0	1	**3/5**
Bachert C. *et al., 2022*	1	0	0	1	0	0	1	**3/5**
Peters, A. *et al*., 2023	1	0	0	1	0	0	0	**2/5**
Boiko N. *et al*. 2023	1	0	0	0	0	0	0	**1/5**

Chart 2. Newcastle-Ottawa Scale-Tool used to assess the quality of the study section.

Cohort study			**Haxel *et al*. 2023**
SELECTION	1) Representativeness of the exposed cohort	a) truly representative of the average _____ (describe) in the community	
		b) somewhat representative of the average _____ in the community	
		c) selected group of users eg nurses, volunteers	X
		d) no description of the derivation of the cohort	
	2) Selection of the non exposed cohort	a) drawn from the same community as the exposed cohort	
		b) drawn from a different source	
		c) no description of the derivation of the non exposed cohort	X
	3) Ascertainment of exposure		
		a) secure record (eg surgical records)	X
		b) structured interview	
		c) written self report	
		d) no description	
	4) Demonstration that outcome of interest was not present at start of study	a) yes	X
		b) no	
COMPARABILITY	1) Comparability of cohorts on the basis of the design or analysis	a) study controls for _____ (select the most important factor)	X
		b) study controls for any additional factor (This criteria could be modified to indicate specific.	
OUTCOME	1) Assessment of outcome	a) independent blind assessment	

		b) record linkage	X
		c) self report	
		d) no description	
	2) Was follow-up long enough for outcomes to occur	a) yes (select an adequate follow up period for outcome of interest) - 6 months	X
		b) no	
	3) Adequacy of follow up of cohorts	a) complete follow up - all subjects accounted for	X
		b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select anadequate %) follow up, or description provided of those lost)	

Resultados

All Works analyzed populations with CRS, containing nasal polyps or not, as well as being or not associated with comorbidities such as asthma, allergic conditions or fungal etiology (Chart 3).

Chart 3. Brief summary of the works analyzed and the main results found. (n=10).

Author and year	Design	Sample and Scenario	Objective	Main results
Jonstam K, *et al.*, 2018	Randomized, double-blind, placebo-controlled, parallel-group study.	Patients aged 18 to 65 years with bilateral nasal polyposis and chronic sinus disease were selected. After 4 weeks of treatment with mometasone furoate nasal spray (MFNS; 100 mg/nostril twice daily), 60 patients were randomly assigned (1:1) to receive a 600 mg loading dose of dupilumab followed by 16 weeks of continuous treatment with either 300 mg of dupilumab (n = 30) or placebo (n = 30). Mometasone furoate nasal spray was applied continuously throughout the study, and inhaled therapies for asthma control were also permitted in patients with this comorbidity.	To report the effects of Dupilumab on total IgE levels and inflammatory markers, mainly type 2 and eosinophilic, in nasal secretions and polyps of patients with Chronic Rhinosinusitis with Nasal Polyps.	Treatment with Dupilumab was associated with a significant decrease in biomarkers of type 2 inflammation, including total IgE in nasal secretions and polyps. These effects of the immunobiological demonstrate that reductions in inflammatory biomarkers were also accompanied by consonant improvements in sinonasal symptoms and polyp reduction, as assessed by nasal endoscopic examinations and computed tomography scans.
Bachert C, *et al.*, 2019	Randomized, double-blind, placebo-controlled study.	The study enrolled 60 patients aged 18 to 65 years during a 4-week run-in period followed by a 16-week blinded treatment period. Inclusion criteria were bilateral nasal polyps and at least 2 symptoms of chronic rhinosinusitis, with or without prior intranasal	To analyze the clinical effects of Dupilumab in patients with Chronic Rhinosinusitis with nasal polyps and comorbid asthma.	Adding Dupilumab to treatment with Mometasone Furoate nasal spray for 16 weeks reduced the size of nasal polyps and improved asthma control, lung function and health-related quality of life in patients compared to those who received placebo alone.

		corticosteroid treatment in the last 2 months before screening. Patients were randomized 1:1 to receive placebo or 300 mg of dupilumab weekly, in addition to mometasone furoate nasal spray applied for 16 weeks.		
Bachert C, *et al.*, 2019	Multicenter, multinational, randomized, double-blind, placebo-controlled study. It combined two studies carried out in approximately 26 countries.	Patients over 18 years of age with symptoms of CRS and bilateral nasal polyps, who had used systemic corticosteroids 2 years prior to the study or who had previously undergone nasal surgery. Patients were divided into two groups, one that received 300mg Dupilumab every 2 weeks and the other placebo group. In SINUS-52, patients received 300mg of subcutaneous Dupilumab for 52 weeks and in SINUS-24, patients received it for an additional 24 weeks.	To evaluate the effect of Dupilumab in patients with CRS with nasal polyps, involving improvement in quality of life, reduction of symptoms and endoscopic evaluation.	Dupilumab reduced the congestive symptoms of CRSwNP, reduced the need for systemic corticosteroid therapy, as well as decreased the indication for sinus-nasal surgery and showed endoscopic improvement after 24 weeks.
Bachert C, *et al.*, 2020	Randomized, double-blind, placebo-controlled study.	It involved 60 patients, who were analyzed for an initial period of 4 weeks, with patients treated with nasal corticosteroid (Mometasone), followed by a period of 16 weeks in which the patients were divided into two groups, one that was treated with Dupilumab – a dose of 600mg followed by doses of 300mg administered weekly for 15 weeks – and another group with Placebo. Within the selected group, there were patients with asthma and nasal polyps, evidenced in previous endoscopy.	To evaluate the impact of Dupilumab on improving patients' quality of life and health, as well as productivity – including abstinence from work/studies – in patients with CRSwNP refractory to the use of nasal corticosteroids.	Dupilumab showed improvements in general health, health perception, physical/psychological and social functioning of patients who received the treatment, when compared with placebo. Dupilumab also proved effective in improving productivity and reducing absenteeism.
Fujieda S, *et al.*, 2021	Multicenter, multinational, randomized, double-blind, placebo-controlled study involving patients with	It involved 488 adults (age ≥ 18 years) with bilateral nasal polyps – endoscopically evaluated – and symptoms of chronic rhinosinusitis, such as nasal congestion. Patients were randomly divided into three groups, one that	To determine the efficacy of Dupilumab in reducing symptoms in patients with CRSwNP with severe symptoms, both with eosinophilia (Eosinophilic CRS) and without eosinophilia.	Dupilumab showed improvement in symptoms and endoscopic evaluation in patients with Eosinophilic CRS – despite not showing a reduction in serum eosinophil count – in addition to being well tolerated by patients.

	CRSwNP with severe and refractory symptoms.	was treated with 300mg of subcutaneous (SC) dupilumab every 2 weeks for 52 weeks, another that was treated with 300mg of SC dupilumab every 2 weeks for 24 weeks and then received doses every 4 weeks for an additional 28 weeks and the third group was treated with placebo every 2 weeks for 52 weeks.		
Bachert C, *et al.*, 2021	Double-blind, placebo-controlled study conducted in the USA and Europe.	Patients aged 18–75 years with bilateral nasal polyps and a history of systemic corticosteroid use or sinonasal surgery. Patients were divided into two groups, one receiving 30 mg of subcutaneous Benralizumab every 4 weeks (3 doses) and then doses every 8 weeks – a total of 52 weeks.	To evaluate the action of Benralizumab in reducing eosinophil counts and reducing obstructive symptoms of CRSwNP.	Benralizumab reduced the obstructive symptoms of nasal polyps; it increased the time required for sinonasal surgery when compared with treatment using systemic corticosteroids. Benralizumab also showed improvements in the quality of life of patients with asthma and was able to reduce the basal eosinophil count (anti-IL-5 action).
Bachert C, *et al.*, 2022	Double-blind, randomized, controlled, placebo-controlled study.	The study involved patients over 18 years of age with severe and recurrent symptoms of CRS with polyps who had previously undergone sinonasal surgery. Approximately 70% of the patients had asthma as a comorbidity and 29% had aspirin-exacerbated respiratory disease (AERD). The patients were divided into two groups: one group receiving 100 mg of mepolizumab every 4 weeks for 52 weeks and the other group receiving placebo.	To evaluate the benefits of Mepolizumab in the endoscopic improvement of nasal polyps and obstruction symptoms, as well as to evaluate the number of asthma exacerbations, AERD and the need for systemic corticosteroid therapy based on baseline eosinophil counts.	Mepolizumab reduced the risks of sinonasal surgery in patients with/without comorbid asthma or AERD and reduced the need for systemic corticosteroids, especially in patients with high eosinophil counts (>300 cells/mL). In addition, Mepolizumab reduced the number of asthma exacerbations in patients.
Haxel, B, *et al.*, 2023	Cohort study, non-randomized and uncontrolled.	Seventy patients with refractory Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) were selected, in which 49 patients received Dupilumab and 21 patients received Omalizumab for three and six months of treatment in 3 health centers in Germany. Patients who had received	To gather data on the efficacy of the immunobiologicals Dupilumab and Omalizumab in the treatment of patients with severe and/or refractory CRSwNP to conventional treatments.	After 6 months of using immunobiologicals, patients showed improvement in all aspects evaluated, even after the first 3 months of treatment. Among them, there were improvements in olfactory function in two-thirds of patients evaluated by the "Sniffin' Sticks" test, improvements in the

		monoclonal antibody treatment in the last two years and with hypersensitivity to any of the immunobiologicals were also excluded.		severity of nasal symptoms evaluated by means of the visual analogue scale (VAS) and an increase in quality of life measured by the SNOT-22 scores. In addition, there was a reduction in polyp scores by the Lildholdt classification.
Peters A, *et al*., 2023	*Post hoc* analysis of phase III, randomized, double-blind, placebo-controlled studies (SINUS-24 and SINUS-52).	In SINUS-24, patients were randomized 1:1 to receive either 300 mg of dupilumab subcutaneously or placebo every 2 weeks for a total of 24 weeks. In SINUS-52, patients were randomized 1:1:1 to receive either 300 mg of dupilumab every 2 weeks for 52 weeks, 300 mg of dupilumab every 2 weeks for 24 weeks and then every 4 weeks through week 52, or placebo. In both studies, patients received 100 micrograms of mometasone furoate nasal spray twice daily.	To investigate the safety and efficacy of the immunobiological Dupilumab in patients with severe CRSwNP with or without allergic rhinitis.	Dupilumab improved nasal symptoms and systemic and nasal biomarker levels at week 24 in patients using the immunobiological, regardless of the presence or absence of allergic rhinitis. In addition, it significantly reduced the need for nasal corticosteroids and/or sinonasal surgery.
Boiko N, *et al*. 2023	Observational, prospective, comparative study.	The study involved the observation of 19 patients with CRSwNP and comorbid asthma who were refractory to treatment using corticosteroids. The patients were divided into two groups, one with 10 patients who received treatment with Dupilumab 300mg SC every 2 weeks and another with 9 patients who received Reslizumab to treat comorbid asthma (3mg/kg/day for 4 weeks). The patients were treated for a period of 24 weeks.	To analyze the efficiency of targeted therapy in patients with CRSwNP and comorbidities – such as asthma.	Treatment with Dupilumab significantly reduced congestive symptoms and the need for corticosteroid therapy, and improved quality of life (improved sleep and ability to engage in physical activities) in Group 1. Reslizumab was able to improve CRSwNP symptoms and reduce asthma relapses in patients in Group II. Among the study groups, the therapy had a more pronounced effect on patients in Group I than on those in Group II.

All the analyzed works were carried out outside of Brazil, mainly in the United States and Europe. One of the selected articles brought together two studies (SINUS 24 and SINUS 52) that were conducted in Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Poland, Romania, Ukraine, Russia, United Kingdom and the United States – SINUS 24 – as well as Argentina, Australia, Belgium, Canada, Chile, Israel, Mexico, Portugal, Russia, Spain, Sweden,

Turkey, Japan and the United States – SINUS 52 and involved about 184 hospitals totaling more than 720 patients[12].

In relation to the types of studies, 08 randomized clinical trials were analysis[1-3,8,9,11,12], a cohort[6] and observational comparative work[10].

The main immunobiologics addressed in the works were Dupilumab [2,3,6,7,8,9,10,12], Mepolizumab[1], Benralizumab[11], Reslizumab[10] and Omalizumab[6].

A study that analyzed the effectiveness of using Dupilumab in 60 patients showed an improvement in symptomatic assessment questionnaires (Nasosinusal Outcome Test 22 - SNOT-22) in relation to the placebo group. In approximately 90% of patients, hyposmia/anosmia was controlled; in 77%, nasal congestion; in 33%, purulent rhinorrhea and, in 26.7%, post-nasal drip[9].

In another work[9], the group treated with Dupilumab showed a significant improvement in endoscopic score of nasal polyps ($p<0.001$), in olfactory sensitivity ($p<0.001$), in total score of Lund-Mackay computed tomography ($p<0.001$) and reduction in disease severity ($p<0.001$). In addition, there was also improvement in the total SNOT-22 score at week 16 in patients treated with immunobiological ($p<0.001$), in FEV1 ($p=0.04$) and in the total score of the 5-item Asthma Control Questionnaire (ACQ-5) ($p<0.001$)[9].

A comparative study sought to analyze and compare the effectiveness of Dupilumab and Reslizumab in patients with CRS and comorbid asthma. At the end of treatment, it was evident that patients showed significant improvement in both the symptomatic evaluation scores (SNOT-22) of CRSwNP and in relation to asthma, verified through the increase of forced expiratory volume in the first second (FEV1). Reslizumab was also shown to reduce eosinophilia in the study patients from the first dose due to the fact that Reslizumab binds to IL-5, restricting the activation and time of eosinophil resistance. Dupilumab, in turn, binds to IL-4 and IL-13, inhibiting the inflammatory response of profile II (Th2), decreasing the action of inflammatory mediators, histamine, leukotrienes and chemokines, reducing inflammation[10].

Mepolizumab, an anti-IL-5 and anti-Eosinophilic immunobiologic agent, was shown to be beneficial in the treatment of CRS with comorbid asthma (52.9%) or comorbid AERD (51.1%)[1]. Furthermore, among participants with eosinophilia, Mepolizumab was able to reduce the total count in 49.5% of patients. Regarding the endoscopic evaluation (for evaluation of nasal polyps), there was a reduction in the size of the polyps and symptomatological improvement in more than half of the patients (50.5% n=104 of 206). Taking into account nasal congestion, Mepolizumab was able to reduce this symptom in 60.2% of the patients. There was also a reduction in the risk of nasal surgeries in the group treated with Mepolizumab, especially in participants with high eosinophil counts[1]. Asthma exacerbations were higher in the placebo group than in the Mepolizumab group

(7.4% vs 4.3%) and among the collateral effects of its use, the main ones were headache and nasopharyngitis[1].

Benralizumab was effective in improving the Nasal Polyps Score - NPS, as well as the control of comorbid asthma, evaluated through the 6-item Asthma Control Questionnaire (ACQ-6 - Asthma Control Questionaire 6-items) within the 40 weeks of treatment. Overall, benralizumab showed good tolerability and presented as main adverse effects of its use, nasopharyngitis, headache and upper airway infections (UAI) – both in the placebo group and in the immunobiological group[11].

When analyzing the effectiveness of Dupilumab and its relationship with eosinophilia, it was evidenced that Dupilumab was able to generate reduction of symptoms of participants with or without ECRS (Eosinophilic Chronic Rhinosinusitis), in addition to generating better score in the nasal polyps scores (NPS) and SNOT-22, in addition to nasal congestion control. However, in this study, there was no clinically relevant interaction between the use of Dupilumab and the reduction of eosinophil count. Among the side effects of medication use, the most common was nasopharyngitis[12].

In another research[6], at first, no serious side effects occurred during initiation of therapy with the monoclonal antibodies Dupilumab and Omalizumab. Before the beginning of treatment, 87% of patients had anosmia, 11% hyposmia and 2% normosmia. After the treatment period for six months, these values changed to 30% with anosmia, 43% hyposmia and 27% normosmia. Positive results, improvements in clinical parameters and quality of life were more pronounced with the use of Dupilumab than with Omalizumab.

The efficacy of Dupilumab was described[7] in patients with severe CRSwNP with or without Allergic Rhinitis (AR) in Phase III SINUS-24/SINUS-52 studies. The analysis involved 724 patients of which 338 (46.7%) had concomitant AR and, at that time, the proportions of patients who received placebo (n=131/286 [45.8%]) and Dupilumab (n=207/438 [47.3%]) were established. The use of the immunobiologic showed a significant increase in forced expiratory volume in the first second (FEV1) and in the 6-item Asthma Control Questionnaire (ACQ-6) observed at week 24 compared to placebo. Moreover, Dupilumab reduced not only the need for systemic corticosteroids and nasal sinus surgery, but also reduced levels of inflammatory biomarkers. Discontinuation due to the appearance of adverse effects was higher in the placebo group, with nasopharyngitis being the most frequent event.

The study of inflammatory biomarkers was also evaluated [8] associated with the use of Dupilumab. Reductions in the concentration of Eosinophilic Cationic Proteins (ECP), eosinophil marker, nasal secretion of eotaxin-3 and total IgE were also observed. Compared to placebo, the

group that was treated with Dupilumab presented similar and even lower concentrations of inflammatory markers at week 16of the study. A limitation for this study was the small number of patients for the analysis of secretions and biopsy of nasal tissue. In patients who underwent follow-up biopsy, there was improvement in radiographic measurements, including the total Lund-Mackay score, the percentage of maxillary sinus occupied by the disease, the SNOT-22 score, the severity of symptoms evaluated by visual analog scale and the sensitivity of smell assessed by UPSIT ($p<0.05$ for all parameters including total IgE levels and eotaxin-3)[8].

All studies were sponsored by pharmaceutical companies, which included Glaxo Smith Kline (GSK) and Sanofi.

Discussion

CRS has as a striking feature the inflammation mediated by several cytokines – such as IL-4, IL-5, IL13 – and IgE immunoglobulins, which are also part of the inflammatory cascade of other diseases such as Asthma, Aspirin-Exacerbated Respiratory Disease (AERD) and Allergic rhinitis, usually comorbid in CRS[2,7]. The use of immunobiologics inhibits the signaling of interleukins, causing them not to trigger inflammatory response – mainly the Profile Th2 or Type II, very common in CRSwNP[2]– besides assisting in the treatment of comorbidities that share the same inflammatory cascade[2].

Among the immunobiologics, there is Dupilumab, a monoclonal antibody that inhibits the signaling of interleukins 4 and 13 (IL-4, IL-13) and thus can inhibit the inflammation Th2 profile. Its use is associated with the improvement of smell, reduced hyposmia/anosmia and their recurrence, as well as rhinorrhea[2]. There was also significant reduction in the risk of sinonasal surgery for nasal polyps and asthma exacerbations in patients who received Dupilumab[2,9,10]. Another interesting point was the improvement in quality of life and scores that evaluate the symptomatology of CRS as SNOT 22[8-10,12]. When compared to the treatment with nasal corticosteroids (Mometasone), Dupilumab showed superior outcomes in endoscopic, radiological, clinical and patient reports[2]. Among the adverse effects of using Dupilumab, studies showed that the main ones were nasopharyngitis, headache and local pain at injection sites[2,3,7,8,12].

Benralizumab is another monoclonal antibody produced in the ovarian cells of Chinese mice that is able to bind to the alpha subunit of IL-5 receptors, being able to rapidly decrease the count of eosinophils and basophiles in the blood stream, acting in a way that stops the inflammation[9]. Benralizumab was able to facilitate the endoscopic evaluation of patients with CRSwNP, and significantly increase the quality of life of patients with reduced symptoms – evaluated through the

SNOT-22 questionnaire[11]. Regarding tolerability, benralizumab was well tolerated, with adverse effects ranging from mild to moderate and having as more common reactions headache and upper airway infections – the latter being less common - and no clinically relevant complaints about pain at the site of drug application[11].

Mepolizumab, another monoclonal antibody studied in this work, also has anti-IL-5 action (similar to Benralizumab) and is used in diseases such as eosinophilic asthma, granulomatosis, eosinophilic polyangiitis. Mepolizumab was shown to be a safe drug, but with few patients (5% of the patients studied) presenting asthma exacerbations, but with mild intensity, and among the adverse effects of its use, only nasopharyngitis, headache and pain at the sites of application were evidenced. Regarding the benefits of its use, Mepolizumab was able to reduce the need for sinonasal endoscopic surgeries, reduce the intensity of nasal congestion symptoms, and improve smell[1].

Reslizumab, another drug that acts by preventing the binding of IL-5– similar to Benralizumab and Mepolizumab – also significantly alleviated symptoms of nasal congestion and rhinorrhea, in addition to the decrease of eosinophilia – which brings benefits for patients with Comorbid Eosinophilic Asthma[10]. The study analyzed does not report any adverse effects relevant to the use of Reslizumab for the treatment of CRS.

Omalizumab is an anti-IgE antibody that was also approved for severe CRSwNP in August 2020. In the cohort study of Haxel *et al*.[6] there was no difference in relation to general resistance to the response to treatment with this immunobiological and Dupilumab. Although the effects of Dupilumab outperformed those of Omalizumab for some scores, such as SNOT-22 and VAS, which did not result in a significantly higher overall response. Therefore, the reduction of symptoms in CRSwNP with the use of Omalizumab was also significant for the treatment of patients living with this disease.

It is important to note that, since there is a management of a range of complex information, associated with the short time for the analysis of studies and the elaboration of the text, there are limitations in the development of the systematic review. Furthermore, there is the possibility of the existence of biased works that may become little effective or ineffective for certain populations, including Brazil, with a view to the specific geolocation of studies carried out by researchers and the societies involved.

Among other limitations of this systematic review is the predominance of a same group of authors in the results obtained after the application of the methodological design and sponsorship of all studies by pharmaceutical laboratories.

Conclusion

CRS is a disease that impairs the quality of life of patients, such as recurrence and prolonged usual treatment, which in many cases is not sufficient for remission of the condition. Treatment with immunobiology showed that the antagonism to the action of interleukins and immunoglobulin E (IgE) generates clinical benefits - such as improvement of congestive symptoms, rhinorrhea, in the size of the polyps and comorbid symptoms of asthma, for example - laboratory, with the reduction of eosinophilia and inflammatory markers, as well as benefits in complementary examinations (sinonasal endoscopies, biopsies, computed tomography and evaluative questionnaires).

Author contributions

All authors approved the final version of the manuscript and declared themselves responsible for all aspects of the work, including ensuring its accuracy and integrity.

Conflict of interest

The authors have no conflicts of interest to declare.

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