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Review

Biological Treatments and Surgical Interventions for Chronic Rhinosinusitis with Nasal Polyps: A Systematic Review of Clinical Outcomes

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Abstract: Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is a chronic inflammatory condition of the nasal and paranasal sinus mucosa with nasal polyp formation. This systematic review evaluated the efficacy and safety of biological therapies, including omalizumab, mepolizumab, and benralizumab, compared with endoscopic sinus surgery (ESS) in CRSwNP management. A literature search using the PubMed, Scopus, and Web of Science databases identified five studies that met the inclusion criteria. The studies included randomized controlled trials and observational studies assessing biological therapies or ESS in adults with CRSwNP. The primary outcomes were nasal polyp score (NPS), nasal congestion score, Sinonasal Outcome Test (SNOT-22), and adverse events. Omalizumab showed significant improvements in NPS, nasal congestion score, and SNOT-22 scores compared to placebo, with sustained effects in an open-label extension study. Mepolizumab significantly reduced SNOT-22 scores, improved lung function, and decreased blood eosinophil counts and systemic corticosteroid use in patients with severe eosinophilic asthma and CRSwNP. Benralizumab improved NPS and nasal blockage scores compared to placebo, with effects varying by comorbidities and baseline characteristics. ESS with medical therapy showed better SNOT-22 scores than medical therapy alone, though not reaching the minimal clinically important difference. Biological therapies and ESS were well tolerated, with adverse events comparable to those of the placebo. This review demonstrates the effectiveness of biological therapies and ESS in managing CRSwNP, particularly in severe cases of the disease. Further research is needed to evaluate the long-term efficacy, safety, and cost-effectiveness of these interventions in CRSwNP management.

Keywords: Chronic Rhinosinusitis with Nasal Polyps; Omalizumab; Mepolizumab; Benralizumab; Endoscopic Sinus Surgery

1. Introduction

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is a subclass of chronic rhinosinusitis marked by chronic inflammation of the nasal and paranasal sinus mucosa with nasal polyp formation. This condition imposes substantial clinical, humanistic, and economic burdens, significantly impacting quality of life, including physical health, mental well-being, and sleep [1].

CRSwNP affects 1–4% of the general population, with a higher occurrence in adults and males [1]. Its pathophysiology includes genetic, environmental, and immunological components. The condition is driven by type 2 (Th2) inflammation, characterized by elevated levels of cytokines, such as interleukin 4 (IL-4), IL-5, and IL-13, along with increased eosinophils [1, 2]. Although tissue eosinophilia is significant in CRSwNP, it is not universal, complicating uniform diagnostic criteria [2].

Symptoms include nasal blockage, anosmia, nasal discharge, facial discomfort or pressure, and post-nasal drip. Diagnosis is primarily clinical, based on a symptom duration exceeding 12 weeks and physical examination. Imaging and nasal endoscopy can confirm the presence of polyps and assess the extent of the disease [3].

The management of CRSwNP initially involves intranasal corticosteroids (INCS) and saline nasal irrigation. For unresponsive patients, treatment options include oral corticosteroids and biological therapies targeting CRSwNP-specific inflammatory pathways [1, 3]. Mepolizumab and dupilumab have demonstrated efficacy in reducing sinus surgery needs and improving outcomes [4, 5]. Severe cases may require surgical intervention, particularly endoscopic sinus surgery [1, 4].

CRSwNP is prone to recurrence, even after surgery. Long-term management with medications and lifestyle modifications is crucial for symptom control and prevention of exacerbations. Ongoing research has explored improved treatments and insights into the underlying mechanisms, with recent studies highlighting the role of fibroblasts in CRSwNP-specific inflammatory pathways as potential therapeutic targets [6].

Given the high recurrence rates and adverse effects of existing treatments, there is a critical need for effective and safe therapies that target the underlying type 2 inflammatory disease pathophysiology [1]. A comprehensive understanding of the multifaceted nature of CRSwNP will enhance management strategies and improve the quality of life of the affected individuals.

CRSwNP is characterized by complex immune responses, epithelial barrier defects, genetic factors, and microbial interactions. This analysis draws from recent studies to elucidate the mechanisms underlying this condition.

A predominant Th2 immune response characterizes CRSwNP, featuring increased levels of IL-4, IL-5, and IL-13. These molecules facilitate eosinophilic inflammation by recruiting, activating, and sustaining eosinophils, which release cytotoxic proteins that damage tissue and sustain inflammation [1, 7, 8]. The cytokine landscape in CRSwNP is enriched in epithelial cells, fibroblasts, and inflammatory cells [7].

Patients with CRSwNP often exhibit a compromised nasal mucosal epithelial barrier, enabling increased penetration of allergens, microbes, and pollutants that perpetuate chronic inflammation. Injured epithelial cells secrete cytokines like thymic stromal lymphopoietin, IL-25, and IL-33, which stimulate Th2 responses and contribute to innate lymphoid cell development [8–10].

Staphylococcus aureus plays a significant role in CRSwNP, with enterotoxins acting as superantigens that stimulate immune cells and enhance Th2 cytokine production. This bacterium affects mucosal barrier function and promotes Th2 inflammation through epithelial-derived cytokines [8, 11]. Dysbiosis of the nasal microbiota is associated with persistent inflammation, and alterations in the microbiota composition may indicate CRSwNP recurrence [11].

Genetic predispositions that affect immune regulation and epithelial integrity increase susceptibility to CRSwNP Environmental factors such as allergens, pollutants, and smoking exacerbate the condition by interacting with genetic factors and compromising the epithelial barrier [1, 9].

Fibroblasts play a crucial role in CRSwNP inflammatory processes by producing extracellular matrix components and cytokines involved in tissue remodeling and polyp formation, thus representing a potential therapeutic target [6]. Although less prominent than eosinophils, neutrophils contribute to inflammation by releasing pro-inflammatory cytokines and enzymes, enhancing Th2 inflammation, and making it more resistant to steroid therapy [9, 12].

Understanding the pathophysiology of CRSwNP is essential for developing targeted therapies. Current treat-

ments aim to reduce inflammation and polyp size using corticosteroids and biologics that target specific Th2 pathway components. Biologics such as dupilumab, mepolizumab, and omalizumab have demonstrated efficacy in alleviating symptoms by targeting specific inflammatory cytokines [13]. Ongoing research into CRSwNP mechanisms may lead to more effective and personalized treatment options, addressing epithelial barrier dysfunction and the roles of fibroblasts and neutrophils in disease pathology.

INCS plays a crucial role in the treatment of CRSwNP owing to its strong anti-inflammatory properties. These medications function by suppressing the generation of inflammatory cytokines and chemokines, leading to decreased eosinophilic inflammation and improved epithelial barrier function [14, 15]. Consequently, this results in diminished polyp size and improvement of symptoms such as nasal blockage and olfactory dysfunction [16]. The therapeutic advantages of INCS include substantial symptom alleviation and prevention of nasal polyp recurrence, particularly with consistent use [14].

Nevertheless, patient responses to INCS vary, and some individuals may require supplementary treatments, such as oral corticosteroids or biologics, to achieve optimal symptom management [1, 13]. Adherence to daily usage is essential for efficacy, and proper administration techniques enhance drug delivery to the target areas [14].

1.1. Current Treatment Strategies for CRSwNP

Managing CRSwNP requires a comprehensive strategy that focuses on inflammation control, symptom relief, and prevention of polyp recurrence. This approach combines drug therapies, surgical procedures, and lifestyle adjustments customized to each patient's condition severity and treatment response.

1.1.1. Medication-Based Approaches

Nasal CS spray serves as the primary treatment for CRSwNP and effectively reduces inflammation by limiting eosinophil infiltration and cytokine production. This action leads to polyp size reduction and improvement in symptoms like nasal blockage and loss of smell [1, 9]. Consistent and proper applications are essential for obtaining the best results [17].

Systemic CS are administered for brief periods to manage severe symptoms or acute flare-ups, offering quick relief through significant inflammation reduction [14, 15]. However, their use is typically limited to short courses because of potential systemic adverse effects [16].

Biologics, such as dupilumab, mepolizumab, and omalizumab, target specific inflammatory mediators in CRSwNP, including IL-4, IL-5, and IgE [13, 18]. These treatments are particularly valuable for patients with severe CRSwNP unresponsive to conventional therapies, demonstrating effectiveness in decreasing polyp size, enhancing quality of life, and reducing the need for surgery [13, 18].

Nasal Saline Rinses aid in removing mucus and allergens, improving mucociliary clearance, and reducing symptom intensity [9].

1.1.2. Surgical Options

Endoscopic Sinus Surgery is recommended for patients with severe CRSwNP who show inadequate response to medical treatments. The procedure involves polyp removal and opening of sinus passages to restore normal drainage and airflow, significantly alleviate symptoms, and improve the quality of life [1, 17]. However, polyp recurrence remains a possibility, necessitating ongoing medical management [1].

1.1.3. Lifestyle and Environmental Adjustments

Minimizing exposure to known allergens and irritants can help control symptoms and prevent exacerbations [11].

Smoking intensifies inflammation and can reduce treatment effectiveness, making smoking cessation a crucial part of management [11].

1.1.4. Continuous Monitoring and Care

Monitoring disease progression and treatment efficacy is crucial for adjusting therapeutic strategies as needed [1].

Informing patients about the chronic nature of CRSwNP and the importance of treatment adherence improves outcomes [1].

Ongoing studies are aimed at exploring new therapeutic targets and enhancing the understanding of the underlying mechanisms of CRSwNP. This includes investigating the role of fibroblasts and epithelial barrier dysfunction in disease pathology, potentially leading to more individualized treatment approaches.

By integrating these diverse treatment strategies, healthcare providers can effectively manage CRSwNP, reduce the symptom burden, and enhance patients' quality of life. Continued research and development of targeted therapies shows promise in addressing the complex pathophysiology of CRSwNP more effectively.

1.2. Role of biologics in CRSwNP

Biological therapies have emerged as a crucial element in the treatment of CRSwNP, especially in severe or resistant cases. These treatments focus on specific cytokines and immune pathways involved in the type 2 inflammatory response characteristic of CRSwNP, thereby providing novel approaches for effective disease control.

1.2.1. Mechanism of Action

Biologics are antibodies designed to target and neutralize specific cytokines or receptors involved in the type 2 immune response, including IL-4, IL-5, IL-13, and IgE, which play key roles in eosinophil recruitment and activation. By interfering with these pathways, biologics decrease eosinophilic inflammation, a central aspect of CRSwNP pathophysiology [9, 10]. This targeted strategy not only reduces polyp size, but also helps improve sinonasal mucosal health, leading to better sinus drainage and significant symptom alleviation, such as improved nasal airflow and reduced congestion [15].

1.2.2. Therapeutic Advantages

For CRSwNP patients who do not respond well to traditional treatments such as intranasal corticosteroids or surgery, biologics have shown effectiveness. Studies on POLYP 1 and POLYP 2 have demonstrated that biologics such as omalizumab can significantly decrease nasal polyp size and improve symptom management [16]. Additionally, biologics offer combined benefits for patients with related conditions such as asthma or allergic rhinitis. Mepolizumab and benralizumab, which target IL-5 and its receptor, have been shown to improve both CRSwNP and asthma control, offering a comprehensive treatment approach [19, 20].

Moreover, biologics can reduce the need for surgical procedures. Although endoscopic sinus surgery (ESS) remains an effective option, it carries risks of recurrence and complications. By managing inflammation and decreasing polyp size, biologics help reduce the need for such surgical interventions [21]. Notably, dupilumab, which targets the IL-4 receptor alpha, has shown significant efficacy in reducing polyp size and improving nasal congestion and sense of smell [13, 22].

The selection of biological therapy should be tailored to each patient's specific inflammatory profile and coexisting conditions, emphasizing personalized treatment approaches. Further research is needed to evaluate the long-term safety and efficacy of biologics, particularly regarding potential immunological effects from extended use [23, 24].

There is also an interest in exploring combination therapies that can enhance the effectiveness of biologics. For instance, combining biologics with other treatment modalities might target CRSwNP-specific inflammatory pathways simultaneously, potentially improving patient outcomes [24, 25]. Furthermore, as our understanding of epithelial barrier dysfunction in CRSwNP increases, there may be opportunities to develop treatments that directly target and restore epithelial function, possibly in conjunction with biologics [10].

Biologics have revolutionized the treatment landscape for CRSwNP by offering targeted and effective options for patients with severe or resistant disease. These therapies show promise for further advancements in personalized medicine, aiming to enhance patient outcomes through precise modulation of the underlying inflammatory processes. Ongoing evaluation of biologics in real-world settings and comparative studies are essential for optimizing their use and integrating them into comprehensive treatment plans for CRSwNP.

The effectiveness of medical interventions extends beyond accurate diagnosis and treatment, encompassing comprehensive long-term patient care plans. Patient commitment to these plans significantly impacts health outcomes, a topic that has been extensively researched regarding medication compliance. Enhancing medication ad-

herence could potentially have a greater impact on health than discovering new treatment options. Nevertheless, many doctors consider nonadherence to prescribed medications as a leading cause of mortality.

1.3. Efficacy and Safety of Biologics and Endoscopic Sinus Surgery

Recent advances in managing CRSwNP include biological therapies and combined endoscopic sinus surgery (ESS) with medical management. This study examined the efficacy and safety of omalizumab, mepolizumab, benralizumab, and ESS with supplementary medical treatment.

Omalizumab, an anti-IgE monoclonal antibody, reduces nasal polyp dimensions and alleviates symptoms, such as nasal obstruction and impaired smell, especially in individuals with concurrent allergic asthma. Trials have shown improvements in nasal polyp scores and quality of life measures, with benefits persisting over extended periods [24, 26].

Mepolizumab, targeting IL-5, has shown effectiveness in reducing polyp size and symptoms in CRSwNP patients with eosinophilic inflammation, also benefiting those with severe eosinophilic asthma [19, 26]. A real-world study revealed reductions in nasal polyp scores, blood eosinophil levels, and systemic corticosteroid usage, enhancing health-related quality of life [19].

Benralizumab, an IL-5 receptor antagonist, induces eosinophil apoptosis and swiftly reduces eosinophilic inflammation and the associated symptoms in patients with CRSwNP. Research has shown its efficacy in decreasing nasal polyp dimensions and improving symptom burden [24].

Biological therapies generally have a favorable safety profile with minor side effects such as injection site reactions and temporary headaches. Serious adverse events are uncommon, but may include hypersensitivity reactions. Current evidence supports the safe use of biologics in CRSwNP management, especially in patients unresponsive to conventional treatments [26].

ESS offers relief for patients with severe CRSwNP, particularly those who are unresponsive to medical therapy alone. This procedure removes nasal polyps and opens sinus passages to enhance drainage and ventilation. Combined with intranasal corticosteroids, ESS significantly reduces nasal polyp recurrence and maintains symptom control [15, 16]. Although generally safe, ESS carries risks typical of surgical procedures. Post-operative care is crucial for preventing recurrence and optimizing outcomes [15, 16].

Biological agents and ESS combined with medical therapy offer complementary approaches for CRSwNP management. Biologics provide a non-surgical option targeting CRSwNP-specific inflammatory pathways, while ESS offers immediate anatomical correction and symptom relief. Treatment selection should be tailored to individual patients based on disease severity, preferences, and responses to previous treatments. Biologics may be advantageous for patients with comorbid conditions such as asthma or contraindications to surgery [4, 14].

Both approaches have demonstrated efficacy and safety for the management of CRSwNP. Biologics offer targeted treatments with minimal systemic side effects, while ESS provides significant anatomical and symptomatic improvements. An integrated treatment plan considering patient-specific factors will yield optimal outcomes in CRSwNP management [25, 26].

The intricate nature of CRSwNP pathogenesis and the varied success rates of treatments highlight the need for comprehensive analysis to evaluate the effectiveness and safety of diverse therapies. As more clinical trials and real-world studies examine biological therapies and surgical procedures, compiling evidence is crucial for guiding clinical decisions.

This systematic review assessed the efficacy and safety of biological treatments, such as omalizumab, mepolizumab, and benralizumab, compared to ESS in treating CRSwNP. By examining data from randomized controlled trials (RCTs) and observational studies, this review offers insights into treatment effectiveness, patient outcomes, and potential risks. Additionally, it investigated how different treatments affect disease recurrence, long-term symptom management, and quality of life.

Given the growing use of biologics and ongoing discussions about their long-term benefits compared with surgery, this review will help identify optimal treatment strategies based on disease severity, patient characteristics, and cost-effectiveness. These results will enhance clinical guidelines and improve personalized treatment approaches for patients with CRSwNP, leading to better disease management and patient outcomes.

This review aimed to evaluate and compare the effectiveness and safety of biological therapies, including omalizumab, mepolizumab, and benralizumab, with ESS in managing CRSwNP. It aims to examine the effects of these

treatments on clinical outcomes, such as nasal polyp size, nasal congestion, and quality of life, analyze CRSwNP recurrence rates, assess safety profiles by reviewing adverse events and complications, determine patient characteristics influencing treatment response to inform individualized strategies, and compile evidence from RCTs and observational studies to provide insights into optimal CRSwNP management approaches.

2. Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. An extensive literature search was conducted using PubMed, Scopus, and Web of Science databases. The search used a combination of Medical Subject Headings terms and keywords such as "chronic rhinosinusitis with nasal polyps", "CRSwNP", "biological therapy", "biologics", "omalizumab", "mepolizumab", "benralizumab", "endoscopic sinus surgery", and "treatment outcomes". The search was limited to English-language studies from the database's inception to the most recent date. Boolean operators (AND, OR, NOT) were used to refine the search results. The reference lists of key studies and reviews were manually examined to identify additional relevant articles.

The inclusion criteria were RCTs and observational studies assessing the effectiveness and safety of biological therapies or ESS for CRSwNP. Eligible studies included adult patients (≥18 years) diagnosed with CRSwNP based on clinical, endoscopic, or radiological criteria.

This review used established thresholds for clinical significance to interpret the treatment effects. For the Sinonasal Outcome Test (SNOT-22), a minimal clinically important difference (MCID) of 9 points was used. A change of 1 point in the Nasal Polyp Score (NPS), assessed on a 0–8 scale, is considered clinically significant. For the Nasal Congestion Score (NCS), changes of 0.5 points on a 0–3 scale are meaningful. A reduction in systemic corticosteroid use or avoidance of surgery during follow-up indicated better disease management. These thresholds were used to interpret the results. These studies reported at least one relevant clinical outcome, such as the NPS, SNOT-22, NCS, systemic corticosteroid requirements, or need for surgical intervention.

Only studies with a minimum follow-up period of 24 weeks were included. The review excluded case reports, reviews, letters, editorials, conference abstracts, studies with incomplete data or a lack of a control/comparator group, and non-English publications.

This review examined pharmacological interventions that underwent rigorous scientific evaluations and employed robust methodologies. A systematic approach was used to extract data, including key variables, such as study design, number of participants, intervention types, primary and secondary endpoints, and statistical relevance. The main objective was to identify treatments that showed significant clinical benefits in decreasing nasal polyp size, enhancing sinonasal function, and reducing related complications.

A multidisciplinary group of specialists in rhinology, pharmacology, and systematic review methods independently performed the literature screening, data extraction, and quality evaluation. Quality assessment was conducted using established instruments, including the Cochrane Risk of Bias Tool for RCTs and Newcastle-Ottawa Scale for observational research. The team worked together to compile the findings and create a final report following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Any disagreements were addressed through group discussions, and decisions were reached by consensus.

Two independent reviewers screened the article titles and abstracts. Full-text assessments were conducted for potentially eligible studies, and disagreements were resolved through consensus or consultation with a third reviewer. The data extraction included study characteristics, patient demographics, baseline characteristics, intervention details, and primary and secondary outcome measures. Adverse events and safety outcomes were also documented.

A comprehensive evaluation of the risk of bias was conducted for studies included in a systematic review that examined six key areas: selection bias (encompassing random sequence generation and allocation concealment), performance bias (focusing on participant and personnel blinding), detection bias (assessing outcome assessment masking), attrition bias (evaluating outcome data completeness), reporting bias (examining the reporting of all prespecified outcomes), and other biases (including additional risks such as funding bias or study-specific issues). Each study received a rating of Low Risk (1), Some Concerns (2), or High Risk (3) in accordance with the Cochrane Handbook for Systematic Reviews of Interventions. For non-RCTs, the ROBINS-I Tool was used to address confounding factors, participant selection, intervention classification, deviations from intended interventions, missing data, out-

come measurements, and reporting bias. Two independent reviewers carried out the assessment process, and any disagreements were resolved through discussion or consultation with a third reviewer. This meticulous approach ensures a transparent and reliable study evaluation.

Ethical approval was not required for this study as it was based on previously published data. However, all included studies were evaluated for adherence to ethical standards, including patient consent and institutional review board approval where applicable. This methodological approach ensures a thorough and transparent evaluation of the efficacy and safety of biological therapies and ESS for CRSwNP, offering clinically relevant insights into optimal treatment strategies.

3. Results

The initial literature search yielded 114 results, with 88 articles excluded because they did not meet the inclusion criteria. After excluding 19 articles due to insufficient data or conclusions, 26 articles were thoroughly examined. Full-text access for two of the remaining seven studies was unattainable despite multiple attempts, leaving five studies for a systematic review [27–31]. **Figure 1** illustrates the selection process and **Table 1** lists the five studies included [27–31].

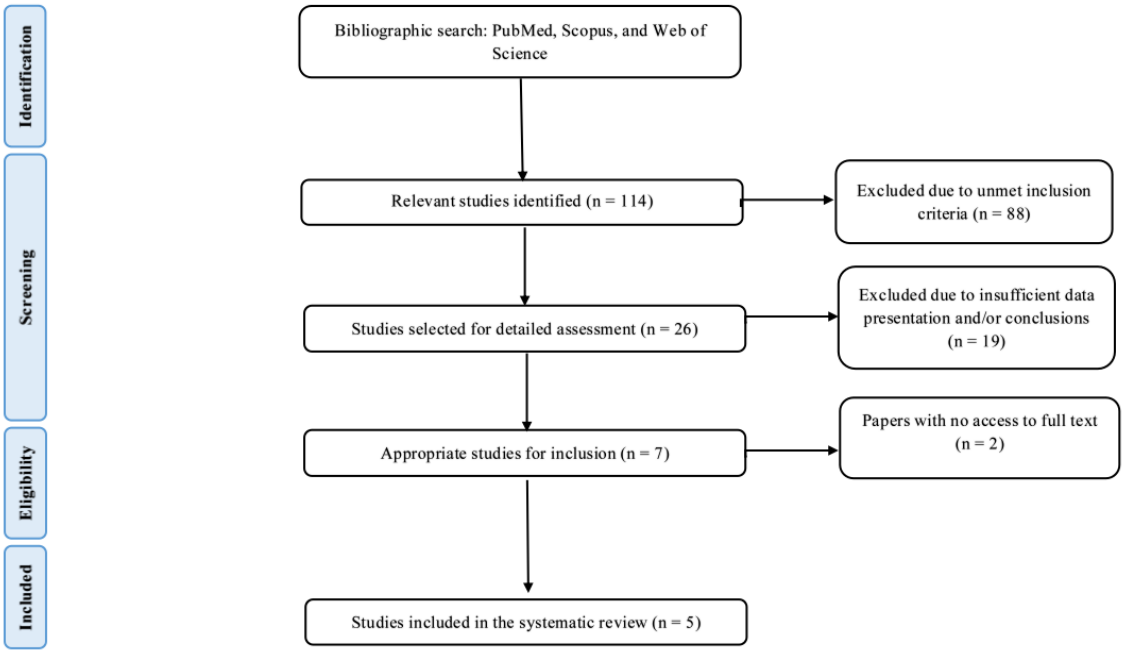

Figure 1. Flow Diagram of Literature Search and Study of Selection for Systematic Review (PRISMA Flow Chart).

This systematic review included RCTs and observational studies from real-world settings to assess the effectiveness and safety of biological treatments (omalizumab, mepolizumab, and benralizumab) and ESS combined with medical therapy for CRSwNP. The number of participants ranged from 44 to 413 with follow-up durations ranging from 24 weeks to 12 months.

Recent studies have highlighted the effectiveness of biological treatment and ESS in managing CRSwNP. A study by Bachert et al. found that benralizumab notably enhanced nasal polyp scores and reduced nasal obstruction compared with placebo [27]. Two phase 3 trials revealed that omalizumab led to considerable improvements in endoscopic, clinical, and patient-reported outcomes [28], with ongoing benefits observed in a 28-week open-label extension study [29]. Additionally, mepolizumab has shown the potential to decrease systemic corticosteroid usage among patients with CRSwNP [30]. A RCT indicated that ESS combined with medical therapy was more effective than medical therapy alone, although the difference did not reach the MCID [31]. These specific therapies and surgical approaches provide new alternatives for treating CRSwNP, especially in patients who do not respond to conventional treatment. However, further research is needed to gather long-term data and to identify biomarkers

for optimal treatment selection.

Table 1. Characteristics of Selected Studies on the Evaluating Treatment Strategies in Patients with CRSwNP [27–31].

Study Details	Intervention	Study Design	Sample Size	Primary Outcome	Outcome Improvement	Safety	Follow-Up Duration
Bachert et al. [27]	Benralizumab	Randomized controlled trial	413	NPS, Nasal Blockage	NPS, Nasal Blockage improved (P ≤ 0.005); Nominal improvement in sense of smell (P = 0.003)	Similar adverse events between omalizumab and placebo.	40 weeks
Gevaert et al. [28]	Omalizumab	Phase 3, randomized, placebo-controlled trials (POLYP 1, POLYP 2)	265	NPS, NCS	NPS: –1.08 vs. 0.06, –0.90 vs. –0.31 (P < 0.0001); SNOT-22: –24.7 vs. –8.6 (P < 0.0001)	Similar adverse events between omalizumab and placebo.	24 weeks
Gevaert et al. [29]	Omalizumab	Open-label extension	249	NPS, NCS	Further improvements in NPS, SNOT-22 maintained up to 52 weeks; worsening post-discontinuation but remained above baseline.	Similar safety profile; no new signs.	52 weeks
Detoraki et al. [30]	Mepolizumab	Prospective observational study	44	SNOT-22, TENPS, %FEV1	SNOT-22 reduced from 51.5 to 29.7 (P < 0.001); TENPS from 2.88 to 1.77; Improved ACT and %FEV1	Well tolerated, reduced blood eosinophils.	12 months
Lourijsen et al. [31]	ESS + Medical Therapy	Multicenter randomized controlled trial	234	SNOT-22	SNOT-22: 27.9 (SD 20.2) vs. 31.1 (SD 20.4); Adj. Mean Diff. –4.9 (95% CI –9.4 to –0.4)	Minor epistaxis, Gastrointestinal issues; 1 unrelated death due to congestive heart failure.	12 months

ESS: Endoscopic sinus surgery; NPS: Nasal polyp score; NCS: Nasal congestion score; SNOT-22: Sinonasal outcome test; TENPS: Total endoscopic nasal polyp score; %FEV1: FEV1/FEV1 Forced Expiratory Volume; ACT: Asthma control test.

3.1. Omalizumab Effectiveness

The POLYP 1 and POLYP 2 phase 3 trials assessed the effectiveness of omalizumab in patients with severe CRSwNP who were not adequately managed with intranasal corticosteroids. Omalizumab showed significant improvements over placebo in the Nasal Polyp Score (NPS) (–1.08 vs. 0.06, P < 0.0001; –0.90 vs. –0.31, P = 0.0140), NCS (–0.89 vs. –0.35, P = 0.0004; –0.70 vs. –0.20, P = 0.0017), and SNOT-22 scores (–24.7 vs. –8.6, P < 0.0001; –21.6 vs. –6.6, P < 0.0001) [28]. An open-label extension study demonstrated sustained improvements, with continued omalizumab use leading to further reduction in disease severity [29]. Patients who stopped treatment experienced some symptom return but remained better than that at baseline. The safety profile of omalizumab was similar to that of placebo.

3.2. Mepolizumab Effectiveness

A 12-month real-world study involving 44 patients with severe eosinophilic asthma and comorbid CRSwNP evaluated the effect of mepolizumab [30]. The treatment significantly reduced SNOT-22 scores from 51.5 ± 21.2 to 29.7 ± 21.5 (P < 0.001) and improved Total Endoscopic Nasal Polyp Score (TENPS) from 2.88 ± 3.07 to 1.77 ± 2.56 (P = 0.99). Mepolizumab also enhanced lung function (%FEV1) and asthma control test (ACT) scores, while substantially decreasing blood eosinophil counts and prednisone usage.

3.3. Benralizumab Effectiveness

The OSTRO trial examined benralizumab in 413 patients with CRSwNP who remained symptomatic despite intranasal corticosteroid administration [27]. Benralizumab significantly enhanced NPS and nasal blockage scores compared with placebo (P ≤ 0.005). Improvements in SNOT-22 and sense of smell scores were noted, although reductions in systemic corticosteroid use and need for surgery did not reach statistical significance. Subgroup analysis indicated that the treatment effects varied based on comorbid asthma, previous surgeries, sex, body mass index, and baseline eosinophil levels. Benralizumab was well tolerated, with a safety profile comparable to that of placebo.

3.4. ESS Plus Medical Therapy Effectiveness

A multicenter RCT compared ESS combined with medical therapy with medical therapy alone in 234 patients with CRSwNP [31]. At 12 months, the ESS group showed a lower mean SNOT-22 score (27.9 ± 20.2) than the medical therapy group (31.1 ± 20.4), with an adjusted mean difference of –4.9 (95% CI –9.4 to –0.4) favoring ESS. However, this did not meet the MCID of 9 points. Adverse events were similar between the groups, and no treatment-related deaths were reported.

3.5. Safety Outcomes

Biological therapies and ESS were generally well-tolerated in all studies [27–31]. Adverse events were comparable between the treatment and placebo groups and no new safety concerns were identified. Minor epistaxis, gastrointestinal disturbances, and temporary worsening of symptoms were the most common adverse events. One unrelated death was reported in the ESS study [31].

Targeted biological treatments, including omalizumab, mepolizumab, and benralizumab, have shown substantial improvements in critical clinical outcomes in patients with CRSwNP inadequately managed with intranasal corticosteroids [27–30]. These outcomes include the nasal polyp score (NPS), nasal congestion, and quality of life measures. Omalizumab demonstrated long-lasting effects over 52 weeks [28, 29], whereas mepolizumab and benralizumab effectively decreased polyp size and enhanced sinonasal symptoms [27, 30]. ESS with medical treatment offered additional advantages compared with medical therapy alone [31], although it did not reach the MCID for SNOT-22 assessment. These results indicate that biological therapies and surgical interventions can significantly treat CRSwNP, particularly in severe or treatment-resistant cases.

The quality of methodology in the included studies was assessed using two tools: Cochrane Risk of Bias Tool for RCTs and ROBINS-I tool for observational research. Across domains, the risk of bias fluctuated, with some studies showing low risk, whereas others exhibited unclear or high risk in particular areas. The evaluation focused on six primary categories: bias in selection, performance, detection, attrition, reporting, and other potential sources.

Most RCTs showed low selection bias, as assessed through random sequence generation and allocation concealment (**Figure 2**). Bachert et al., Gevaert et al., and Detoraki et al. clearly described randomization processes and allocation concealment, minimizing systematic differences between groups [27, 28, 30]. Lourijsen et al. and Gevaert et al. had unclear risks due to inadequate reporting of allocation methods [29, 31].

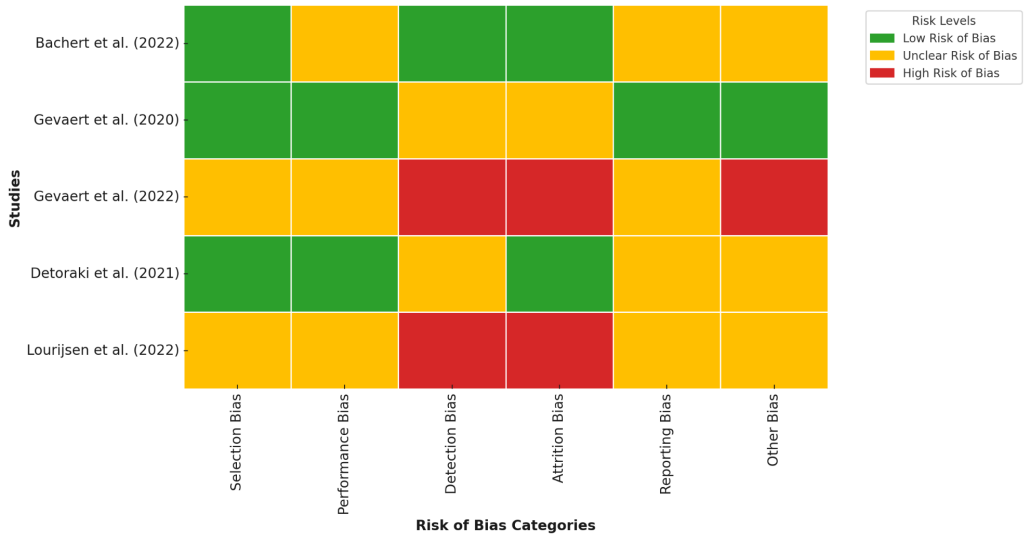

Figure 2. Risk of Bias Assessment in Systematic Review.

Performance bias was low in double-blind RCTs, such as Gevaert et al. and Detoraki et al., effectively blinding participants and researchers [28, 30]. Bachert et al. and Lourijsen et al. had unclear risk due to limited blinding information [27, 31]. Gevaert et al had high risk of performance bias, as its open-label design allowed awareness

of treatment [29].

To mitigate detection bias, blinding of outcome assessors is crucial. Bachert et al. and Detoraki et al. demonstrated low risk by ensuring blinded assessments [27, 30]. Gevaert et al. had unclear risk due to insufficient description [28]. Gevaert et al. and Lourijsen et al. were at high risk, as assessments were not blinded [29, 31].

Attrition bias was low in studies with minimal loss to follow-up, including those by Bachert et al. and Detoraki et al. [27, 30]. Gevaert et al. and Lourijsen et al. had unclear risk due to insufficient disclosure of missing data handling [28, 31]. Gevaert et al. were at high risk, with significant dropout rates without clear explanations [29].

Studies that fully reported pre-specified outcomes, such as Bachert et al. and Gevaert et al., showed low selective reporting bias [27, 28]. Detoraki et al. and Lourijsen et al. had unclear risk, as discrepancies between protocol and reported outcomes were not addressed [30, 31]. Gevaert et al. exhibited high risk of reporting bias, with apparent omission or selective reporting of some secondary outcomes [29].

In Bachert et al. and Gevaert et al., the risk of funding-related bias and confounding factors was minimal owing to comprehensive funding disclosures and robust methodologies [27, 28]. Detoraki et al. and Lourijsen et al. presented an uncertain risk owing to incomplete methodological information [30, 31]. Gevaert et al. exhibited a high risk, with industry sponsorship and open-label design raising concerns about potential bias [29].

Most RCTs showed low or unclear risk of bias in critical areas, such as selection and attrition bias, lending credibility to their results. However, open-label and observational studies have demonstrated a higher risk, particularly in domains related to blinding, attrition, and selective reporting. The primary concern was bias associated with blinding, as many outcomes were subjective and susceptible to the influence of expectations. To enhance the evidence, base for biological therapies and surgical interventions in CRSwNP, future studies should emphasize double-blind designs, comprehensive reporting, and effective management of missing data.

4. Discussion

This review examines the efficacy of biological treatments and ESS in treating CRSwNP. Omalizumab, mepolizumab, and benralizumab effectively reduce polyp size, ease nasal congestion, and enhance quality of life, especially in severe or refractory cases. In contrast, ESS provides substantial symptom relief but does not target the underlying inflammatory processes that lead to disease recurrence.

Biological treatments have garnered interest in targeting CRSwNP-specific inflammatory pathways. The POLYP 1 and POLYP 2 trials showed omalizumab targeting IgE, decreased nasal polyp dimensions, and congestion, especially in individuals with allergic asthma [28, 29, 32]. Mepolizumab, targeting IL-5-mediated eosinophilic inflammation, proved effective in diminishing polyp burden and reliance on systemic corticosteroids, reducing steroid-related adverse effects [30, 33]. Benralizumab, an IL-5 receptor antagonist, induces eosinophil death resulting in smaller nasal polyps and enhanced symptom management [27, 34]. However, the individual responses to benralizumab varied, emphasizing biomarker-guided treatment selection.

Although biological therapies have shown effectiveness, ESS remains crucial for patients with severe CRSwNP who are unresponsive to intranasal and systemic corticosteroids. Research suggests that combining ESS with medical therapy yields better symptom relief than medical therapy alone, although improvement often falls short of the MCID, indicating that some individuals may need additional biological therapy for optimal results. A primary drawback of ESS is its inability to address the underlying immune dysregulation in CRSwNP, which leads to frequent recurrence. Integrating biological therapy with ESS may enhance long-term disease management by targeting both the structural and immunological aspects of CRSwNP.

Biological therapies were generally well tolerated, with adverse event rates similar to those in the placebo groups. Common side effects were mild, including injection site reactions, headaches, and temporary upper respiratory symptoms, whereas serious adverse events were uncommon. This favorable safety profile positions biologics as a viable long-term treatment alternative for patients requiring frequent corticosteroid use or multiple surgeries. In contrast, ESS, while effective, carries surgical risks, such as postoperative bleeding, scarring, and infection. Although no treatment-related deaths have been reported, careful patient selection and postoperative care are crucial for minimizing complications.

This review highlights the importance of personalized treatment for CRSwNP. Biologics offer a non-surgical, targeted method for reducing inflammation and improving sinonasal function, whereas ESS remains valuable for immediate symptom relief in severe cases. It's important to identify predictive biomarkers to customize the biolog-

ical selection for individual patients to ensure maximum effectiveness. Additionally, extended comparative studies evaluating the cost-effectiveness of biologics versus ESS are necessary to inform clinical decision making.

These outcomes align with those of research indicating that biological therapies decrease the need for systemic corticosteroids and surgical procedures in severe CRSwNP patients [4, 5]. As type 2 inflammation drives CRSwNP, biological treatments targeting IL-4, IL-5, and IgE offer a personalized approach that is effective in alleviating nasal and systemic symptoms in affected patients [13].

The management of CRSwNP has evolved, with emphasis on biological therapies targeting Th2 inflammatory mechanisms. This study provides insights into these treatments, particularly biologics, and their effectiveness in managing CRSwNP.

The POLYP 1 and POLYP 2 trials by Gevaert et al. highlighted the advantages of biological therapy for patients with CRSwNP, showing symptom improvements and reduced nasal polyp size [28]. These studies underscore the effectiveness of biologics in patients not managed with conventional therapies [13, 17]. The open-label study of omalizumab confirmed the long-term efficacy and safety of this anti-IgE monoclonal antibody, especially for patients with allergic conditions [9, 17].

Lourijsen et al.'s study compared ESS with medical therapy, showing significant symptom and quality of life improvements, particularly for severe cases or those unresponsive to medical management [10]. This supports surgical intervention when medical therapy is insufficient [1].

The OSTRO trial on benralizumab, an anti-IL-5 receptor monoclonal antibody, showed reductions in nasal polyp size and symptoms, supporting its use in eosinophilic CRSwNP [15]. Detoraki et al.'s study on mepolizumab also demonstrated potential in reducing nasal polyps and symptoms in patients with CRSwNP and severe eosinophilic asthma [16, 19].

Epithelial barrier dysfunction in CRSwNP pathogenesis is crucial because epithelial cells contribute to chronic inflammation [9, 10]. Treatments like corticosteroids and biologics aim to counteract these effects, reducing symptoms and nasal polyp recurrence [14, 35].

Most RCTs minimize selection bias through rigorous random sequence generation and allocation concealment. Bachert et al. and Gevaert et al. clearly outlined their randomization methods [27, 28]. Some studies, such as that by Lourijsen et al., showed unclear risks due to inadequate documentation of allocation procedures [31]. Observational studies are more prone to selection bias due to non-randomized participant assignments.

Blinding participants and personnel are vital for reducing performance bias. Double-blind RCTs, such as Gevaert et al. and Detoraki et al., showed a low bias risk due to effective blinding [28, 30]. Open-label studies, such as Gevaert et al.'s extension trial, demonstrated a high-performance bias risk as participants and researchers were aware of treatment assignments [29]. Outcome assessor blinding varied across the studies.

Bachert et al. and Detoraki et al. successfully implemented blinded evaluations, minimizing detection bias [27, 30]. Gevaert et al. and Lourijsen et al. failed to adequately describe blinding methods for outcome assessors, resulting in a high risk of bias [29, 31]. Given that many CRSwNP outcomes are subjectively evaluated, unblinded assessments may overestimate the treatment effects.

Attrition bias was low in studies with minimal dropout rates and proper handling of missing data, as demonstrated by Bachert et al. [27]. Several studies, such as that by Gevaert et al., showed high attrition rates with insufficient explanations for missing data [29]. This issue is particularly concerning in longitudinal studies, as attrition can compromise result validity.

Studies that fully disclosed pre-specified outcomes, such as Bachert et al., had a low selective reporting bias risk [27]. Gevaert et al.'s study indicated selective reporting, as some secondary outcomes were omitted from the final analysis [29].

Funding bias was evident in studies sponsored by pharmaceutical companies, particularly those evaluating biologics. Gevaert et al. showed a high risk of bias due to industry funding [29]. Observational studies are susceptible to confounding bias due to a lack of randomization and control for external factors. Although many studies have used statistical adjustments, residual confounding factors cannot be ruled out.

Research studies have exhibited varying bias risk levels, with RCTs generally showing reduced risks compared to observational studies. Key concerns centered on blinding techniques, dropout rates, and selective reporting. These limitations should be considered when interpreting the results, as biases may have influenced the effect sizes and conclusions. To enhance evidence quality, future studies should prioritize double-blind design, comprehensive

data disclosure, and independent funding. This systematic review incorporates rigorous bias risk assessments, examining current evidence to guide clinical decisions regarding CRSwNP treatment while acknowledging potential shortcomings.

5. Conclusions

This review highlights the effectiveness and safety of biological therapies and ESS for the management of CRSwNP. Biological agents, such as omalizumab, mepolizumab, and benralizumab, show significant reductions in nasal polyp size, improved symptom scores, and enhanced quality of life, especially for severe or refractory CRSwNP. ESS provides quick symptom relief but does not address the underlying immune dysregulation, leading to recurrence and requiring ongoing medical intervention.

Despite substantial benefits, the high costs and long-term administration of biological treatments present accessibility challenges. Combining ESS with targeted biological therapy may offer optimal long-term disease management for selected patients. Treatment response variability underscores the need for personalized approaches, guided by inflammatory phenotyping and biomarker assessments.

Biological agents have revolutionized CRSwNP treatment by offering a targeted approach to control inflammation and reduce the disease burden. Further research is needed to optimize treatment selection, evaluate long-term safety, and determine cost-effectiveness. Integrating evidence-based medical therapies with surgical intervention can enhance the outcomes and improve the quality of life of patients with CRSwNP.

5.1. Limitations

This systematic review has several limitations. The diversity in research methodologies, participant numbers, and observation periods affects the comparability of results. The limited sample size may restrict its broader applicability. The quality of evidence varied, with some studies showing an unclear or high risk of blinding, participant dropout, and selective data reporting. Open-label designs could lead to performance bias, whereas inadequate blinding of outcome evaluators raises concerns about detection bias. Variations in treatment approaches and outcome measurements complicate comparisons. Some studies used standardized nasal polyp scores and symptom severity scales, whereas others relied on patient-reported outcomes. Potential publication bias exists as favorable results are more likely to be published, inflating perceived treatment effectiveness. Long-term safety data for biological therapies are scarce. Short-term research shows promising safety profiles; however, the consequences of extended biological use require further study. This review did not extensively analyze economic factors, such as the cost-effectiveness of biologics compared with ESS, making it challenging to assess the financial viability of long-term biological therapy.

5.2. Recommendations

Future studies should prioritize well-designed, double-blind, randomized controlled trials with larger participant pools and uniform outcome metrics. Long-term follow-up research is crucial to assess the durability of therapeutic benefits and safety profiles of biological treatments. Comparative studies evaluating biologics against ESS, particularly in terms of cost-effectiveness and recurrence rates, could provide valuable insights into the treatment protocols.

Subsequent studies should explore predictive markers to identify patients who are most likely to respond positively to biological therapy. Personalized treatment approaches based on inflammatory phenotyping and biomarker analysis may enhance outcomes and minimize unnecessary exposure to costly interventions. Additionally, empirical studies involving diverse patient populations will help to validate the effectiveness of biologics and ESS in real-world settings.

Future research should include economic assessments to evaluate the financial viability of the biologics. Given the high costs associated with long-term biologics use, cost-effectiveness analyses are essential to guide healthcare policies and reimbursement decisions.

Author Contributions

Conceptualization, T.H., K.A., and H.M.; methodology, S.M., M.H., and L.F.; validation, A.M., S.A., and M.A.; formal analysis, R.A., and S.A.; resources, F.D., and A.A.; data curation, S.J., and B.A.; writing—original draft preparation, T.H., K.A., and H.M.; writing—review and editing, S.M., M.H., L.F., A.M., S.A., and M.A.; supervision, R.A., S.A., F.D., A.A., S.J., and B.A.. All authors have read and agreed to the published version of the manuscript.

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