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Review

Advances in Biologics for Rhinology: Evidence and Prospects in Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) and Allergic Rhinitis

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Abstract: Chronic rhinosinusitis with nasal polyps (CRSwNP) and allergic rhinitis (AR) are common upper-airway inflammatory disorders that often coexist, significantly decrease quality of life, and recur even when treated with intranasal or systemic therapy or surgery. Growing mechanistic insights, such as the role of type 2 inflammation driven by epithelial "alarmins" (TSLP, IL-25, IL-33) and downstream cytokines (IL-4/IL-13, IL-5), together with IgE-mediated effector pathways, have led to the accelerated clinical use of targeted biologics. Here, we summarize the shared immunopathogenesis of CRSwNP and AR, highlight treatable endotypes and practical biomarkers (e.g., blood eosinophils, total IgE, FeNO, and disease-specific symptom and quality-of-life scores), and map these features to therapeutic targets. We summarize evidence for approved agents, including anti-IgE omalizumab; anti-IL-5/IL-5R therapies mepolizumab, reslizumab, and benralizumab; and anti-IL-4R therapy dupilumab, focusing on clinically significant outcomes such as nasal polyp burden, nasal obstruction, olfaction, SNOT-22/TNSS improvement, reduction in systemic corticosteroid use, surgery rates, safety, and limitations. Given that many patients have multimorbidity with asthma or atopic dermatitis, we also outline how unified airway management can guide multidisciplinary decision-making and the use of shared endpoints. Practical considerations such as initiation criteria, response assessment, treatment switching, and economic or access barriers are summarized to inform real-world implementation and future research.

Keywords: Chronic Rhinosinusitis with Nasal Polyps; Allergic Rhinitis; Biologics; Monoclonal Antibodies; Immune Mechanisms; Precision Medicine

1. Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) and allergic rhinitis (AR) are among the most prevalent chronic inflammatory diseases affecting the upper airways [1]. These conditions often share overlapping clinical features and exert significant adverse effects on the patient's quality of life. They are characterized by persistent inflammation of the nasal and sinus mucosa and are frequently associated with type 2 (T2) immune responses, including eosinophilic infiltration, elevated IgE levels, Th2 cells, and group 2 innate lymphoid cells (ILC2s) [2,3]. The coexistence of CRSwNP and AR with lower airway diseases such as asthma further complicates clinical management [4–7]. Traditional therapeutic approaches have relied on corticosteroids, antihistamines, and surgical interventions [8]. However, a subset of patients exhibits refractory disease, underscoring the need for more targeted

therapeutic options.

Advances in immunology have demonstrated that T2 inflammation, driven by cytokines such as IL-4, IL-5, and IL-13, plays a central role in disease pathogenesis [9]. This understanding has facilitated the development of biologic therapies targeting specific molecules and pathways involved in T2 inflammation [10,11]. For example, the IL-4 receptor α antagonist dupilumab attenuates T2 signaling and significantly improves sinonasal outcomes in patients with CRSwNP [12–15]. Similarly, anti-IL-5 biologics, including mepolizumab and reslizumab, reduce eosinophilic inflammation and nasal polyp burden [13–15]. Omalizumab, an anti-IgE monoclonal antibody, has also been shown to improve sinonasal symptoms regardless of allergic status [15]. Ongoing research into biomarkers, disease endotyping, and novel therapeutic agents continues to refine personalized treatment strategies, with the goal of improving efficacy, safety, and quality of life in patients with CRSwNP and AR [16,17].

2. Immune Pathogenesis of CRSwNP and AR

2.1. Th2-Type Inflammatory Response as the Core Mechanism in CRSwNP and AR

Both chronic rhinosinusitis with nasal polyps (CRSwNP) and allergic rhinitis (AR) are characterized by predominant Th2-type inflammation. Th2-type inflammatory responses are a major driver of both diseases. In CRSwNP, multiple studies have shown higher levels of Th2-associated cytokines, such as interleukin (IL)-4, IL-5, and IL-13, in nasal polyp tissue compared with controls, leading to marked eosinophilic infiltration and increased local IgE synthesis [18,19]. The upregulation of these cytokines induces the recruitment, activation, and survival of eosinophils, which are key effector cells involved in tissue damage and remodeling. IL-5 is critical for eosinophil differentiation and longevity, and its increased expression is characteristic of type 2 inflammation in CRSwNP [20].

Allergic rhinitis is also driven by Th2-skewed immunity, with increased production of IL-4 and IL-13 inducing B-cell class switching to IgE, which subsequently sensitizes mast cells and basophils and promotes classical allergic inflammation [21]. Polyclonal IgE production in CRSwNP and oligoclonal, antigen-specific IgE in AR may contribute to differences in disease severity and recurrence rates between the two conditions.

The nasal epithelium releases key cytokines, including thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, in response to environmental triggers such as allergens, pollutants, and pathogens [22,23]. These cytokines act as alarm signals that activate group 2 innate lymphoid cells (ILC2s) and Th2 cells, thereby initiating and amplifying type 2 immune responses. For example, TSLP expression is significantly increased in the sinonasal mucosa of patients with CRSwNP, particularly in those with eosinophilic inflammation, and is involved in the initiation and perpetuation of Th2-dominated immune responses [22]. IL-33 and IL-25 also contribute to the activation and expansion of ILC2s, which produce large amounts of IL-5 and IL-13 independent of antigen stimulation, thereby propagating eosinophilic infiltration and mucus hypersecretion. This interplay between epithelial cells and immune cells forms a self-reinforcing loop that sustains chronic inflammation in CRSwNP and AR and may explain resistance to standard therapies in some patients.

Recent studies have shown that epithelial barrier dysfunction facilitates the entry of allergens and pathogens, leading to increased upstream release of epithelial cytokines and enhanced Th2 inflammation [24]. Tight junction dysfunction observed in both CRSwNP and AR increases epithelial permeability and immune activation. Overexpression of epithelial mediators such as cystatin SN (CST1) further triggers and aggravates type 2 inflammation. Restoration of epithelial barrier function may therefore represent a useful adjunctive strategy for the treatment of both diseases [25]. Given the similarity of the epithelial–immune axis in CRSwNP and AR, therapies targeting epithelial-derived cytokines or improving barrier integrity may be beneficial in both conditions, particularly in patients with severe or refractory disease.

Furthermore, interactions between Th2 cells, ILC2s, and other immune subsets, including regulatory T cells (Tregs) and B cells, further modulate the chronicity and severity of inflammation. In CRSwNP, reduced frequency and impaired function of Tregs within polyp tissue are associated with unchecked Th2 responses and increased eosinophilic infiltration [26,27]. B-cell activation and subsequent IgE production are prominent in both AR and CRSwNP; however, the underlying mechanisms may differ, with extrafollicular pathways being more prominent in CRSwNP [21]. Frequent colonization with Staphylococcus aureus can act as a superantigen in CRSwNP, stimulating polyclonal IgE production and further amplifying Th2 inflammation [28]. These findings suggest that Th2-type immune responses are not only central but also multifaceted, involving complex interactions among epithelial, innate,

and adaptive immune components.

Collectively, the evidence indicates that Th2-type inflammation plays a pivotal role in both CRSwNP and AR, with epithelial cells serving as important amplifiers of these immune responses. While downstream effects such as eosinophilic infiltration and IgE synthesis have been well established, upstream regulation by epithelial cells and innate lymphoid populations represents potential therapeutic targets. As research continues to elucidate these pathways, targeting Th2-type inflammation at multiple levels may improve outcomes in chronic inflammatory diseases of the upper airways.

The cascade of type 2 inflammation, including key cytokines (IL-4, IL-5, and IL-13) and effector cells (eosinophils), is visually summarized in **Figure 1**.

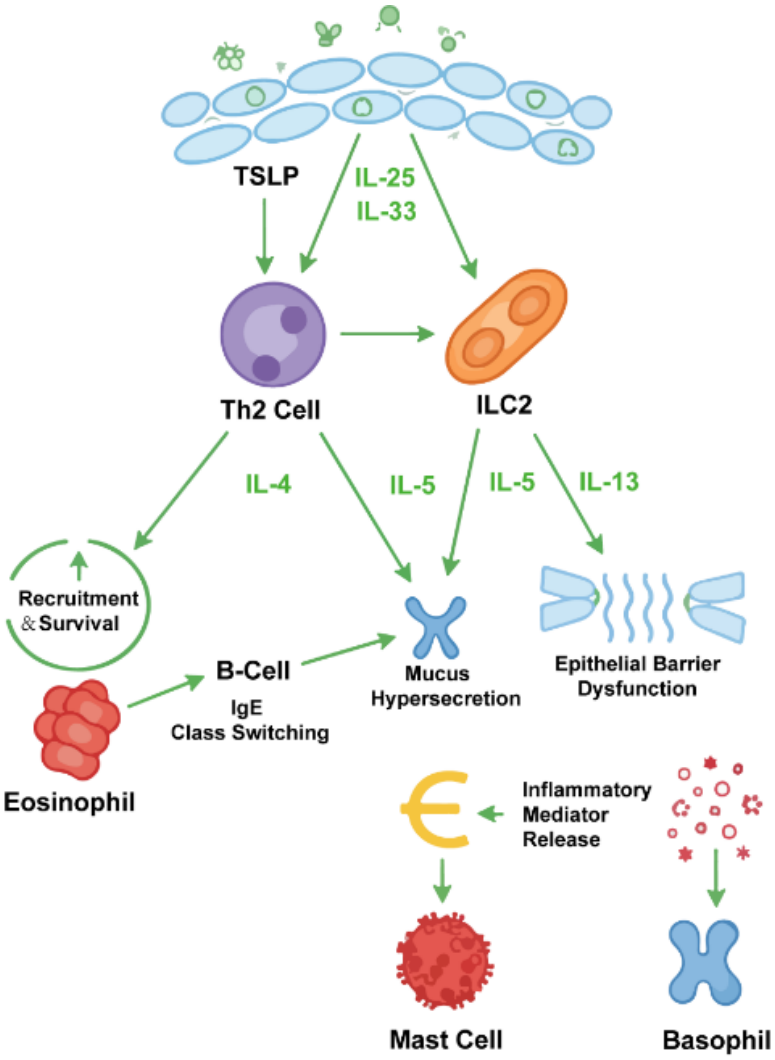

Figure 1. Pathogenic mechanisms of type 2 inflammation in chronic rhinosinusitis with nasal polyps (CRSwNP) and allergic rhinitis.

Environmental stimuli activate nasal epithelial cells, resulting in the release of the alarmins thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33. These alarmins activate T helper type 2 (Th2) cells and group 2 innate lymphoid cells (ILC2s), leading to the production of the type 2 cytokines IL-4, IL-5, and IL-13. IL-5 promotes eosinophil recruitment and survival, whereas IL-4 and IL-13 induce B-cell IgE class switching, mucus hypersecretion, and epithelial barrier dysfunction. IgE subsequently binds to mast cells and basophils, triggering the release of inflammatory mediators that contribute to chronic sinonasal inflammation and tissue remodeling. Green arrows indicate activation or promotion.

2.2. Identification and Mechanisms of Key Molecular Targets

Identification of key molecular targets has changed the therapeutic landscape of chronic rhinosinusitis with nasal polyps (CRSwNP) and allergic rhinitis (AR). Immunoglobulin E (IgE) plays a major role in immediate hypersensitivity reactions in AR and in a large proportion of patients with CRSwNP. Elevated IgE levels activate mast cells and basophils upon allergen exposure, leading to degranulation and rapid release of histamine and other pro-inflammatory mediators. This cascade underlies acute AR symptoms and contributes to persistent inflammation in CRSwNP, particularly in allergic patients. Clinically, anti-IgE monoclonal antibodies such as omalizumab reduce symptom severity and improve quality of life in severe allergic asthma and CRSwNP [29]. Patient selection based on endotype, particularly type 2 inflammation with elevated IgE levels, is critical for optimal biologic therapy outcomes [30]. The variable response to anti-IgE therapy in CRSwNP may partly reflect disease heterogeneity, suggesting that IgE-driven mechanisms are more prominent in certain patient subgroups.

Interleukin-5 (IL-5) is another key cytokine responsible for the differentiation, survival, and recruitment of eosinophils, which are major effector cells in type 2 inflammation and central contributors to CRSwNP pathogenesis. Elevated tissue and peripheral eosinophil counts are associated with disease severity, polyp burden [31], and risk of recurrence. The development and clinical application of IL-5–targeting biologics, such as mepolizumab and benralizumab, have demonstrated significant reductions in nasal polyp size, symptom scores, and the need for surgical intervention in patients with eosinophilic CRSwNP [32]. However, clinical trial and real-world data indicate that blockade of the IL-5/IL-5 receptor axis alone may be insufficient in some patients due to the complex and multifactorial nature of CRSwNP pathophysiology [33]. While IL-5 is essential for eosinophilic inflammation, additional cytokines and cellular interactions may modulate disease expression and treatment response, suggesting that combination or upstream targeting strategies may be required in refractory cases.

Interleukins IL-4 and IL-13, produced by Th2 lymphocytes and group 2 innate lymphoid cells, play critical roles in inflammation and tissue remodeling in CRSwNP and AR [34]. IL-4/IL-13 signaling promotes B-cell class switching to IgE and induces epithelial changes that contribute to chronic inflammation and nasal polyp formation [35]. The clinical success of dupilumab, an IL-4 receptor antagonist that blocks both IL-4 and IL-13 signaling, highlights the therapeutic relevance of this pathway. Dupilumab has demonstrated substantial efficacy in reducing polyp size and improving olfactory function and nasal congestion in CRSwNP, as well as in treating comorbid atopic dermatitis and asthma [7]. Recent molecular studies suggest that IL-4/IL-13 signaling promotes lipid peroxidation and epithelial dysfunction in nasal polyps, linking this pathway to disease pathogenesis at the tissue level [36]. These findings indicate that targeting the IL-4/IL-13 axis not only suppresses inflammation but may also partially reverse tissue remodeling, supporting its role in comprehensive disease modification.

Emerging upstream molecular targets, including interleukin-25 (IL-25), thymic stromal lymphopoietin (TSLP), and interleukin-33 (IL-33), collectively referred to as epithelial alarmins, are being explored in next-generation biologic therapies. These cytokines are rapidly released by the airway epithelium in response to environmental stressors and act upstream to initiate and amplify type 2 immune responses through activation of dendritic cells and innate lymphoid cells [37]. TSLP has been implicated in the maintenance of type 2 inflammation and immune homeostasis at mucosal surfaces [38], and clinical trials targeting TSLP are currently underway for several allergic diseases [37]. Similarly, IL-33 has been shown to enhance Th2 cytokine production and promote tissue eosinophilia in refractory airway disorders. Targeting epithelial alarmins may therefore exert broader immunomodulatory effects and offer therapeutic benefit for patients who respond inadequately to downstream cytokine blockade.

In summary, the identification and mechanistic characterization of IgE, IL-5, IL-4/IL-13, and epithelial alarmin pathways have informed the rational design of biologic therapies while underscoring the importance of endotype-based patient stratification. Given the complexity and heterogeneity of CRSwNP and AR, future biologic strategies are likely to incorporate multi-target approaches and principles of personalized medicine to achieve optimal disease control and long-term remission.

3. Evidence-Based Data of Biologics in the Treatment of CRSwNP

3.1. Anti-IgE Monoclonal Antibody (Omalizumab)

Omalizumab is a humanized monoclonal antibody targeting IgE. Clinical trials and real-world studies have shown that omalizumab improves sinonasal symptoms and reduces polyp burden. In the pivotal phase 3 POLYP 1

and POLYP 2 trials, omalizumab in combination with intranasal corticosteroids significantly improved nasal polyp score (NPS), nasal congestion, and patient-reported quality-of-life measures such as the Sino-Nasal Outcome Test-22 (SNOT-22). At week 24, the mean reduction in NPS was −1.08 and −0.90 in the two trials, respectively, and SNOT-22 scores were significantly improved by 24.7% and 21.6% compared with placebo [39]. Open-label extension studies further confirmed the durability of these benefits over 52 weeks, with sustained objective and subjective improvement [40].

The therapeutic utility of omalizumab extends to patients with CRSwNP regardless of allergic status or comorbid asthma. Post hoc analyses of the POLYP 1 and POLYP 2 trials and their open-label extensions showed that omalizumab improved sinonasal outcomes, including reductions in NPS, nasal congestion, and SNOT-22 scores, in patients with or without physician-reported allergic comorbidities, with or without asthma, and across a range of baseline IgE levels and blood eosinophil counts [10]. These findings suggest that omalizumab may be effective across multiple CRSwNP phenotypes and not only in patients with classic allergic disease. Real-world studies have also demonstrated that omalizumab significantly reduces episodes of acute sinusitis and the need for sinus surgery, indicating potential benefit in refractory cases [41]. Based on these data, omalizumab may be considered a frontline biologic option for patients with CRSwNP who have failed conventional therapies, particularly those with comorbid asthma or evidence of type 2 inflammation.

Similar efficacy has been demonstrated in phase 3 studies of other biologics, such as dupilumab in the SINUS-52 trial. Patients treated with dupilumab showed marked improvements in nasal polyp score and nasal congestion within the first few months of treatment, along with clinically meaningful improvements in quality-of-life measures. In studies of omalizumab, patients with elevated IgE levels and comorbid allergic disease also demonstrated significant clinical improvement and a reduced need for systemic corticosteroids, which represent typical responder profiles observed in clinical practice.

From a clinical perspective, a representative scenario involves a patient with severe, refractory CRSwNP, frequent postoperative recurrence, and comorbid allergic disease who experiences rapid symptom relief and a reduced requirement for systemic corticosteroids following initiation of biologic therapy.

Mechanistically, omalizumab binds to free IgE, thereby preventing its interaction with the high-affinity IgE receptor (FcεRI) on effector cells such as mast cells and basophils. This neutralization of circulating IgE leads to downregulation of FcεRI expression and subsequent attenuation of downstream allergic inflammation [42]. Recent studies have shown that IgE not only drives mast cell and basophil activation but also promotes eosinophil migration within nasal polyps through upregulation of CCR3, a process that is effectively inhibited by omalizumab [43]. Baseline levels of IgE-positive cells in nasal polyp tissue have been shown to predict clinical response to omalizumab and may serve as a potential biomarker for patient selection and treatment monitoring [43]. These findings further support the pathogenic role of IgE in CRSwNP and the rationale for anti-IgE therapy.

Beyond improvements in sinonasal symptoms and polyp size, omalizumab has demonstrated significant benefits in related domains, including olfactory function, sleep quality, and overall health status. Data from randomized controlled trials and real-world studies indicate that patients receiving omalizumab experience meaningful improvements in sleep quality, as assessed by the SNOT-22 sleep domain and the Medical Outcomes Study Sleep Scale, as well as improved self-reported health status [44]. In addition, omalizumab has been associated with improvements in anxiety symptoms in patients with CRSwNP and comorbid asthma, although its effect on depressive symptoms appears limited [45]. These multidimensional benefits contribute to overall quality-of-life improvement and may reduce the broader disease burden in this patient population.

Although omalizumab is generally well tolerated, with a safety profile comparable to placebo in clinical trials, its cost-effectiveness and optimal positioning among available biologics remain under investigation. Comparative analyses suggest that omalizumab is currently among the more cost-effective biologic options for patients with recalcitrant CRSwNP, although variations in drug pricing, dosing strategies, and patient selection may influence future cost-effectiveness models [46]. Ongoing head-to-head trials, such as the EVEREST study comparing omalizumab and dupilumab, are expected to provide further insight into the relative efficacy and safety of these agents in patients with severe CRSwNP and comorbid asthma [47]. Given the heterogeneity of CRSwNP, continued refinement of biomarker-based patient stratification will be essential to optimize the use of omalizumab and other biologics and to ensure that patients receive the most appropriate targeted therapy for their individual disease profiles.

3.2. Anti-IL-5 and IL-5 Receptor Monoclonal Antibodies (Mepolizumab, Reslizumab, Benralizumab)

Monoclonal antibodies targeting the interleukin-5 (IL-5) pathway, including mepolizumab, reslizumab, and benralizumab, are important therapeutic options for patients with eosinophilic chronic rhinosinusitis with nasal polyps (CRSwNP), particularly those with comorbid asthma driven by chronic eosinophilic inflammation. IL-5–targeting therapies can effectively suppress eosinophil-mediated inflammation in both CRSwNP and severe eosinophilic asthma. Mepolizumab and reslizumab neutralize circulating IL-5, whereas benralizumab targets the IL-5 receptor alpha (IL-5Rα) on eosinophils and induces rapid apoptosis through antibody-dependent cell-mediated cytotoxicity [48, 49]. This mechanistic difference may explain variations in the depth and speed of eosinophil depletion among these agents, with benralizumab often achieving near-complete eosinophil reduction in both blood and tissue.

Clinical trials and real-world evidence demonstrate that anti-IL-5 therapies significantly reduce eosinophil counts in peripheral blood and sinonasal tissue and lead to improvements in symptom burden, nasal polyp size, and quality of life. In a meta-analysis of randomized controlled trials, anti-IL-5 therapies were associated with reductions in nasal polyp score (weighted mean difference: −0.71), nasal congestion, and SNOT-22 scores, as well as improvements in olfactory function [50]. These clinical benefits are also accompanied by reductions in disease recurrence and the need for surgical intervention, particularly in patients with a history of multiple surgeries or repeated systemic corticosteroid use. Treatment efficacy appears most pronounced in patients with elevated blood or tissue eosinophil levels, underscoring the importance of endotype-driven patient selection in CRSwNP [51,52].

Mepolizumab currently has the broadest regulatory approval for CRSwNP, particularly in adult patients, supported by evidence from randomized controlled trials and real-world cohorts [53,54]. Mepolizumab reduces eosinophil infiltration in sinonasal tissue, demonstrates steroid-sparing effects, and decreases the frequency of polyp recurrence and revision surgery. Reslizumab is approved for severe eosinophilic asthma and has shown encouraging results in small cohorts of patients with CRSwNP, with improvements observed in both asthma control and nasal symptoms [9]. Benralizumab, owing to its receptor-targeted mechanism, induces rapid and profound eosinophil depletion, and real-world studies in patients with severe asthma and comorbid CRSwNP have reported significant reductions in polyp size, improvements in SNOT-22 scores, and decreased oral corticosteroid requirements [55,56]. These findings suggest that benralizumab may be particularly beneficial for patients with severe or persistent disease who are inadequately controlled by other biologics.

Overall, the safety profiles of anti-IL-5 and anti-IL-5R therapies are favorable, with adverse event rates comparable to placebo in large-scale meta-analyses [50]. Some differences in infection risk and specific adverse event patterns have been reported, such as numerically higher rates of bronchitis and pneumonia with benralizumab compared with mepolizumab and reslizumab; however, these findings have not reached statistical significance and require further investigation [57]. Long-term data support the continued use of these agents, although careful monitoring for rare or delayed adverse events is advisable, particularly in patients with multiple comorbidities or prolonged treatment duration [58,59].

By consistently reducing eosinophilic burden, improving sinonasal and asthma symptoms, and decreasing the need for systemic corticosteroids and surgery, anti-IL-5 and anti-IL-5R monoclonal antibodies represent a major advance in the management of eosinophilic CRSwNP, especially in patients with coexisting asthma. Future head-to-head comparisons, biomarker-guided treatment algorithms, and consideration of patient-specific factors such as comorbidities, prior biologic exposure, and individual treatment response will be essential for optimizing precision medicine approaches. Integration of these biologics into multidisciplinary care pathways has the potential to substantially improve outcomes for patients with severe, eosinophil-driven upper and lower airway disease.

3.3. Anti-IL-4/IL-13 Monoclonal Antibody (Dupilumab)

Dupilumab, a fully human monoclonal antibody targeting the interleukin-4 receptor alpha (IL-4Rα) subunit, has become the first approved biologic treatment for patients with moderate to severe chronic rhinosinusitis with nasal polyps (CRSwNP) who are refractory to corticosteroids or experience frequent relapse after surgery. By blocking IL-4Rα, dupilumab inhibits both IL-4 and IL-13 signaling, which are key drivers of type 2 inflammation associated with CRSwNP [60,61]. The phase III LIBERTY NP SINUS-24 and SINUS-52 trials demonstrated the efficacy and safety of dupilumab [62]. In these studies, patients with moderate to severe CRSwNP receiving intranasal corticos-

teroids were randomly assigned to subcutaneous dupilumab or placebo. Treatment regimens consisted of biweekly injections for 24 or 52 weeks, with some patients transitioning to monthly dosing after an initial intensive phase.

Clinically, dupilumab has shown rapid and sustained improvements in key disease parameters. In the SINUS-24 and SINUS-52 trials, patients treated with dupilumab demonstrated significant improvements in nasal congestion/obstruction, sense of smell, and nasal polyp score compared with placebo [62]. Imaging outcomes, including sinus opacification scores, also improved, and these benefits were maintained even when the dosing interval was extended [62]. Importantly, dupilumab significantly reduced the need for systemic corticosteroids and sinonasal surgery, with consistent effects observed regardless of asthma status or prior surgical history [63]. Real-world studies and observational cohorts have confirmed these findings, showing significant improvements in quality of life (SNOT-22), olfactory function, and reduced polyp recurrence rates [64–66]. Notably, restoration of olfactory function often precedes visible polyp reduction, suggesting that neural inflammation and epithelial integrity may be directly affected. Early intervention with dupilumab may therefore help prevent irreversible olfactory dysfunction and reduce cumulative disease burden.

Mechanistically, dupilumab disrupts IL-4 and IL-13 signaling by binding to IL-4Rα, thereby preventing downstream activation of STAT6 and sustained type 2 inflammatory responses [60,61]. Both cytokines play critical roles in eosinophil recruitment, IgE class switching, goblet cell hyperplasia, and tissue remodeling, which are hallmark features of CRSwNP. In vitro studies indicate that IL-4, more than IL-13, impairs nasal epithelial barrier function, reduces ciliary motility, and delays wound repair; these effects are reversed by dupilumab, leading to restoration of epithelial function [67]. Dupilumab also reduces local and systemic biomarkers of type 2 inflammation, including eotaxin-3, periostin, thymus and activation-regulated chemokine (TARC), total IgE levels, and mast cell counts in nasal mucosa [68]. These findings support the concept that targeting upstream mediators of type 2 inflammation may result in more effective and durable disease control than inhibition of downstream effectors alone.

The benefits of dupilumab extend beyond polyp reduction and symptom relief to include improvement in common comorbid conditions such as asthma and allergic rhinitis, which frequently coexist with CRSwNP [62,69]. In the SINUS-24 and SINUS-52 trials, patients with comorbid asthma experienced improved lung function and asthma control, further supporting the concept of shared type 2 inflammatory mechanisms across the upper and lower airways. Subgroup analyses demonstrated consistent therapeutic benefits of dupilumab regardless of allergic rhinitis status, prior surgery, or baseline eosinophil levels [63,69]. These findings suggest that dupilumab may be broadly applicable across different CRSwNP endotypes, although predictive biomarkers for optimal patient selection are still under investigation [60]. Given the robust and consistent improvements observed across multiple clinical domains, dupilumab may also reduce healthcare utilization associated with repeated surgery and long-term systemic corticosteroid use.

In summary, dupilumab represents a paradigm shift in the management of moderate to severe CRSwNP, offering rapid and sustained symptom relief, significant reduction in polyp burden, improved quality of life, and a favorable safety profile. Through dual inhibition of IL-4 and IL-13 signaling, dupilumab addresses key upstream mechanisms of type 2 inflammation and provides additional benefits for comorbid atopic diseases. As evidence continues to accumulate, dupilumab is likely to become a cornerstone of personalized treatment strategies for CRSwNP, with the potential to reduce reliance on repeated surgical interventions and prolonged systemic corticosteroid therapy.

3.4. Emerging Targets and Biologics in Development

Recent years have seen significant progress toward novel targets for chronic rhinosinusitis with nasal polyps (CRSwNP), focusing on upstream mediators of type 2 inflammation such as interleukin-25 (IL-25), thymic stromal lymphopoietin (TSLP), and interleukin-33 (IL-33). In contrast to existing biologics targeting downstream cytokines (e.g., IL-4, IL-5, IL-13), these new agents target earlier triggers of the inflammatory cascade and may be more effective for patients with resistant or biologic-insensitive disease. Epithelial alarmins such as TSLP, IL-25, and IL-33 are released from stressed or damaged nasal epithelium in response to environmental stimuli and play roles in immune cell activation and initiation of inflammatory processes in CRSwNP [70]. Targeting these upstream mediators may help dampen self-amplifying loops of type 2 inflammation and tissue remodeling that contribute to polyp formation and disease persistence.

One of the most promising experimental agents is tezepelumab, a human monoclonal antibody against TSLP.

In the phase 3 WAYPOINT trial, tezepelumab significantly improved nasal polyp score, nasal congestion severity, and patient-reported quality of life (SNOT-22) compared with placebo [71]. Post hoc analyses of related studies (e.g., NAVIGATOR and PATHWAY) also suggest that tezepelumab suppresses type 2 inflammatory biomarkers (e.g., eosinophils, FeNO, IL-5, and IL-13) and reduces asthma symptoms in patients with comorbid disease. Moreover, tezepelumab maintained a favorable safety profile, with no increased risk of serious infections or hypersensitivity reactions reported. Although not yet approved specifically for CRSwNP, its upstream mechanism and broad anti-inflammatory effects suggest it could fill critical gaps for patients who are not sufficiently responsive to corticosteroids or currently available biologics. As trials such as ESSENCE advance, they should provide further clarity regarding long-term efficacy, safety, and optimal positioning relative to established monoclonal antibodies.

In addition to TSLP inhibitors, monoclonal antibodies targeting IL-33 and IL-25 are also being developed, and small-molecule approaches are being explored. Janus kinase inhibitors that broadly suppress downstream cytokine signaling have been used in several type 2 diseases and may represent a future option for refractory cases; however, long-term safety, optimal dosing, and positioning relative to biologics in CRSwNP and AR remain under investigation. IL-33, another epithelial alarmin, has been shown to recruit and activate innate lymphoid cells (ILC2s) and Th2 cells, thereby promoting type 2 inflammation in CRSwNP. Early studies of anti-IL-33 agents such as PF-06817024 have shown good tolerability and pharmacodynamic evidence of target engagement in healthy volunteers and CRSwNP patients [72]. Clinical results are still emerging, but these agents may more effectively modulate disease activity upstream in the inflammatory cascade, which could benefit patients with severe or corticosteroid-refractory disease. IL-25–targeted therapies are also being investigated because IL-25 promotes Th2 responses and eosinophilic inflammation. It is possible that blocking multiple alarmins simultaneously, or combining upstream blockade with downstream cytokine inhibitors, could further improve disease control in difficult-to-treat CRSwNP [70].

The rationale for targeting these novel upstream pathways is further supported by single-cell sequencing and spatial transcriptomics studies examining the complex immune–epithelial interactions involved in CRSwNP pathogenesis [73]. These technologies indicate that epithelial barrier dysfunction and dynamic crosstalk between epithelial and immune cells are major drivers of disease progression. These findings suggest that interventions targeting epithelial alarmins may disrupt the initiation and perpetuation of chronic inflammation more effectively than downstream blockade alone. As such, agents directed against TSLP, IL-33, and IL-25 may align with the ongoing shift toward precision medicine in rhinology. With further validation, these therapies could be incorporated into individualized treatment algorithms for patients with distinct endotypes characterized by prominent epithelial–immune dysregulation.

In summary, the clinical development of monoclonal antibodies targeting IL-25, TSLP, and IL-33 offers a new approach for CRSwNP treatment. Early results suggest strong anti-inflammatory activity with promising objective improvements and patient-reported outcomes. As ongoing and future studies clarify long-term effectiveness, safety, and value, these therapies may expand the treatment repertoire for patients with refractory disease or those who do not respond well to currently approved agents. Integration into clinical practice will depend on biomarkers predictive of response, cost-effectiveness, and real-world experience across diverse patient populations.

4. Application and Evidence of Biologics in Allergic Rhinitis

4.1. Role and Evidence of Omalizumab in AR Treatment

Omalizumab is a humanized monoclonal antibody targeting IgE and has been used extensively in seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). Multiple randomized controlled trials and real-world studies show that omalizumab reduces symptom scores and rescue medication use in allergic rhinitis patients who are poorly controlled with standard therapies. For instance, 12 trials found that omalizumab reduced the Daily Nasal Symptom Severity Score by −0.41 points, with greater effects reported in cedar pollen–induced AR than in non–cedar pollen AR. Additionally, omalizumab improved ocular symptoms and quality-of-life scores and decreased the mean daily intake of rescue antihistamines, without a significant increase in adverse events compared with placebo [74]. These findings are supported by prospective clinical studies showing that both short- and long-term omalizumab use leads to marked improvements in nasal congestion, sneezing, and rhinorrhea [75–77], as well as patient-reported quality-of-life measures. Furthermore, omalizumab appears effective in both SAR and PAR, suggesting that its effects may be broadly applicable across different AR phenotypes [78]. Given consistent reductions

in symptom burden and medication requirements, omalizumab may be particularly useful for moderate-to-severe AR not sufficiently controlled by standard treatment.

In addition to its standalone effect, omalizumab has been used as an adjunct to specific immunotherapy (SIT) for AR. Combining omalizumab with allergen immunotherapy has been shown to reduce immunotherapy-related adverse reactions (including systemic allergic reactions and anaphylaxis), thereby improving the safety of SIT [78,79]. This effect may be particularly relevant for patients who are more susceptible to allergic reactions or have experienced suboptimal outcomes. Omalizumab may also improve adherence to immunotherapy regimens by reducing the risk of severe allergic reactions, potentially allowing more aggressive up-dosing or maintenance schedules. Mechanistically, rapid reduction of free IgE may decrease mast cell and basophil activation during allergen exposure and reduce allergic inflammation contributing to SIT-related adverse events [74,78]. This may help bridge patients who otherwise cannot tolerate or complete allergen immunotherapy.

The efficacy of omalizumab in AR is also supported by pharmacoeconomic and real-world evidence. A study of preseasonal omalizumab in AR showed that a single 300 mg injection two weeks before pollen season reduced the mean daily CSMS throughout the pollen season compared with standard medication. Patients treated with omalizumab also had more medication-free days and better control of nasal and eye symptoms, with improvements in quality of life [80]. Pharmacoeconomic studies suggest that at current pricing, omalizumab may not be cost-effective for SAR in general populations, but the incremental cost-utility ratio is more favorable in moderate-to-severe cases [81]. This highlights the importance of appropriate patient selection. Therefore, omalizumab may be best suited for severe patients or those at high risk of complications from conventional treatment, with potential expansion as cost considerations are addressed.

Biomarker studies have also identified potential predictors of response to omalizumab in AR. For example, the ratio of total IgE at week 16 to baseline has been reported to correlate with clinical effectiveness, and a ratio of approximately 2.0 may indicate a higher likelihood of response [82]. This suggests that monitoring IgE kinetics during treatment may help identify responders and guide treatment decisions. In addition, omalizumab binds to circulating free IgE and inhibition of FcεRI expression on effector cells may explain its broad effects across AR subtypes and its ability to reduce both nasal and ocular symptoms [83,84]. Given heterogeneity in AR, biomarker-based approaches combined with clinical evaluation may help optimize patient selection and outcomes.

In summary, omalizumab has proven to be an effective and safe option for seasonal and perennial AR in moderate-to-severe cases that do not respond to conventional therapy. Its use as an adjunct to SIT may provide an additional benefit by improving safety and tolerability, potentially enabling more patients to benefit from disease-modifying immunotherapy. Future work should focus on long-term safety, cost-effectiveness, and personalized medicine approaches.

4.2. Prospects of Dupilumab and Other Biologics in AR

Dupilumab is a fully human monoclonal antibody targeting the interleukin-4 receptor alpha (IL-4Rα). It is an attractive therapy for patients with moderate-to-severe disease and comorbid type 2 inflammatory conditions such as asthma and atopic dermatitis. Multiple clinical studies and systematic reviews show that dupilumab improves nasal symptoms and quality of life in AR patients, including those receiving antihistamines and intranasal corticosteroids [78,85]. In patients with persistent allergic rhinitis, dupilumab reduced total nasal symptoms and improved patient-reported quality-of-life measures, including SNOT-22 [78]. Inhibition of IL-4 and IL-13 signaling supports suppression of type 2 inflammation, which is central to AR pathophysiology [7]. Importantly, studies suggest that these benefits extend to AR patients with comorbid asthma, with improvements in asthma control and rhinoconjunctivitis-specific quality of life, highlighting the link between upper and lower airway disease [86,87].

The benefits of dupilumab in AR involve not only symptom control but also modulation of underlying inflammatory pathways. Transcriptomic analyses in nasal tissue suggest that dupilumab can normalize gene expression signatures in AR and may directly affect disease endotypes [88]. Real-world studies indicate that dupilumab is safe and tolerable in AR patients, including those with multiple comorbidities, with most adverse events being mild and not requiring discontinuation [8,89]. Standard allergy tests such as skin prick testing appear largely unaffected during dupilumab treatment, allowing clinicians to continue monitoring sensitization profiles in treated patients [90]. These findings suggest that dupilumab may be incorporated into individualized treatment algorithms for AR patients with severe, refractory symptoms or significant comorbidities, although long-term cost-effectiveness and

access remain important considerations [91].

Other biologic agents, such as those targeting interleukin-5 (IL-5) and its receptor (mepolizumab, reslizumab, and benralizumab), are under consideration for potential roles in AR, particularly in severe eosinophilic disease. Anti-IL-5 therapies reduce blood and tissue eosinophils and are effective in severe eosinophilic asthma, but evidence for AR is limited and less robust than for dupilumab and omalizumab [78,92]. Current data suggest that anti-IL-5 therapies may be useful in severe, treatment-refractory AR with marked eosinophilia, but additional randomized controlled trials are needed to clarify efficacy and optimal patient selection. The limited real-world experience and lack of regulatory approvals in AR underscore the exploratory nature of anti-IL-5 therapy in this setting [92]. Future adoption will depend on evidence of clinical benefit, safety, and cost-effectiveness relative to existing treatments.

In the future, biologics may be more widely used in AR. Endotyping and biomarker-based stratification may help identify patients who benefit most from targeted agents such as dupilumab [91]. Combination strategies (e.g., biologics plus allergen immunotherapy) may also be considered, with early evidence suggesting improved tolerability and possibly enhanced efficacy in selected patients [93]. However, challenges remain, including long-term safety data, dosing and adherence issues, and cost-effectiveness models to ensure equitable access. Continued development of biologics, including agents targeting upstream mediators of type 2 inflammation, may broaden the therapeutic landscape for AR and provide new options for difficult-to-treat disease [13].

In summary, current evidence suggests that dupilumab can be used safely to improve nasal symptoms and quality of life in AR patients, particularly those with comorbid asthma or severe refractory disease. Anti-IL-5 biologics may be useful for selected patients with severe eosinophilic AR, but their use remains investigational. As research progresses, biologic therapies are expected to play an increasingly important role in personalized AR treatment for patients who do not respond to conventional therapy.

4.3. Indications and Limitations of Biologics in AR

Biologic agents have emerged as promising therapeutic options for allergic rhinitis (AR) patients who do not respond to conventional treatments or who have comorbid asthma or severe eosinophilic inflammation. AR results from complex interactions between epithelial cytokines (TSLP, IL-33, and IL-25) and downstream type 2 pathways (IL-4, IL-5, IL-13, IgE) [23]. Biologics targeting downstream processes (anti-IgE and anti–type 2 cytokines) can be effective in selected AR patients, particularly those with severe asthma and/or marked eosinophilic inflammation [94]. In practice, biologic therapy is generally reserved for severe symptoms refractory to intranasal corticosteroids, antihistamines, allergen immunotherapy, or for patients with severe comorbid asthma and persistent type 2 inflammation.

Biologics also have important limitations. Long-term costs are substantial, and access remains limited in many settings, placing strain on healthcare systems [95]. Long-term safety in AR is not well defined; much of the safety evidence is derived from asthma and other type 2 diseases, and relatively few large-scale, long-duration studies in AR populations are available [94]. This uncertainty necessitates individualized risk–benefit assessment before initiating biologics, particularly where conventional treatments remain effective. Given these considerations, biologics are typically reserved for AR patients with the highest unmet needs (e.g., frequent exacerbations, poor quality of life, and high comorbidity burden).

Another key issue is the limited cost-effectiveness evidence for biologics in AR. Although biologics have transformed the management of severe asthma and other allergic airway diseases, high costs and limited long-term AR-specific outcomes make routine use difficult to justify [94]. In addition, many AR trials have focused on severe, persistent disease or patients with significant comorbid asthma, limiting generalizability to broader AR populations. As more real-world data and head-to-head studies become available, eligibility criteria may be refined, potentially incorporating biomarkers and clinical phenotypes to identify those most likely to benefit.

Finally, the expanding range of biologics raises questions regarding sequencing, combination strategies, and long-term management. Biologics are targeted approaches to immune modulation in AR, but integration into standard treatment algorithms remains under discussion. Development of biosimilars and price reductions may improve access over time; until then, high costs and incomplete long-term safety data will limit use to carefully selected patients with severe, refractory AR and significant comorbid disease.

In summary, biologic agents in AR are primarily indicated for patients with severe, treatment-resistant disease, particularly those with comorbid asthma or pronounced eosinophilic inflammation, but high costs and uncertain

long-term safety currently limit widespread application.

5. Evaluation of the Efficacy and Safety of Biologics

The clinical effects of currently approved biologic agents, such as dupilumab and omalizumab, in reducing nasal polyp burden, improving symptom control, and enhancing quality of life in CRSwNP have been established in randomized controlled trials and real-world studies. Therefore, the following sections focus on evaluation metrics, safety profiles, treatment optimization, and future directions rather than reiterating general efficacy results.

5.1. Clinical Efficacy Evaluation Metrics

Clinical efficacy assessment of biologics in CRSwNP and allergic rhinitis relies on standard, validated outcome measures. Common endpoints include Nasal Polyp Score (NPS), Nasal Congestion Score (NC), olfactory testing (e.g., loss of smell scores or Brief Smell Identification Test), the 22-item Sino-Nasal Outcome Test (SNOT-22), and Total Nasal Symptom Score (TNSS). These measures provide a multidimensional view of disease burden, combining objective assessment (e.g., endoscopic polyp size and appearance) with patient-reported outcomes related to symptoms and quality of life [96]. These endpoints are widely used in trials and real-world studies, facilitating comparisons across interventions and assessment of clinical improvement.

Large randomized placebo-controlled trials (e.g., LIBERTY NP SINUS-24, SINUS-52, POLYP 1/2, SYNAPSE) show that biologics produce substantial reductions in NPS and improvements in NC and SNOT-22, reflecting reduced nasal obstruction and improved health-related quality of life [62, 97–99]. For example, in SINUS-24 and SINUS-52, dupilumab produced mean NPS reductions of more than 2 points compared with placebo, with similar improvements in NC and SNOT-22 above the minimum clinically important difference. Improvements were also supported by gains in olfactory function (subjective and objective) and reductions in TNSS, indicating broad symptom benefit.

In addition to symptom relief, biologics reduce disease recurrence and the need for systemic corticosteroids or revision surgery. Longitudinal studies and meta-analyses show lower relapse rates, reduced polyp regrowth, and sustained improvements in NPS and SNOT-22 [100–102]. The need for systemic corticosteroids or surgical intervention is also reduced compared with placebo or standard medical therapy, suggesting potential modification of disease trajectory and improved long-term control. This is particularly important in patients with asthma or severe type 2 inflammatory signatures, where biologics may also improve lower-airway outcomes and overall quality of life.

While most studies show improvements across these endpoints, response can vary by disease type, baseline severity, and biologic class. For example, dupilumab often shows greater improvements in NPS and NC than mepolizumab or omalizumab in indirect comparisons, consistent with blockade of IL-4 and IL-13 signaling, key drivers of type 2 inflammation in CRSwNP [32, 99]. Non–type 2 or neutrophilic endotypes may respond less, underscoring the importance of endotype-driven patient selection [103]. Given variability in response, integrating multiple clinical measures (NPS, NC, SNOT-22, and olfactory outcomes) into a unified assessment framework may improve evaluation accuracy and guide personalized treatment decisions.

Overall, standardized efficacy endpoints enable objective evaluation of biologic therapy in CRSwNP and allergic rhinitis and support evidence-based decision-making and individualized treatment for severe or refractory disease.

5.2. Adverse Reactions and Safety

With increasing use of biologics in CRSwNP and allergic rhinitis, safety considerations are important. In randomized controlled trials and real-world studies, the most common adverse events are mild to moderate, including injection site reactions, headache, pharyngitis, and transient hypereosinophilia. In a systematic review of 13 studies including 2282 CRSwNP patients treated with biologics, common adverse events included injection site reactions, erythema (9.4%), headache (8.1%), and epistaxis (5.1%). Omalizumab trials also reported headache, nasopharyngitis, and injection site reactions as common events [104]. Mepolizumab and reslizumab studies reported adverse events including headache and infections, with rare reports of epistaxis and asthma-related events [104]. These findings are consistent with large phase 3 trials and meta-analyses showing that most events are non-specific, self-limiting, and rarely lead to discontinuation [105, 106].

Serious adverse events (SAEs) associated with biologics are uncommon. In the SYNAPSE trial of mepolizumab for CRSwNP, on-treatment SAEs occurred at similar rates in the mepolizumab and placebo groups, and none were judged drug-related [107]. Network meta-analyses also report no significant differences in SAEs between biologics and placebo, supporting an overall favorable safety profile [108, 109]. Real-world data are consistent: analyses including 3,921 patients report low discontinuation rates due to adverse events and predominance of mild-to-moderate reactions [105]. In a two-year multicenter study of dupilumab, only 2.4% of patients discontinued therapy due to safety concerns, and most adverse events were mild to moderate [110]. These findings suggest biologics are generally well tolerated, although ongoing pharmacovigilance remains important.

Prolonged biologic use raises theoretical concerns about immunosuppression, infection risk, and rare delayed adverse effects. Most studies have not shown significant increases in infections, but follow-up in many trials and cohorts is limited to 1–2 years. For example, a 12-month real-world study of dupilumab in CRSwNP reported no severe adverse effects requiring rescue treatment [111]. Transient hypereosinophilia has been reported, and rare cases of severe hypereosinophilia leading to discontinuation have been described [112]. In allergic rhinitis, meta-analyses indicate monoclonal antibodies are generally well tolerated without significant increases in total, severe, or serious adverse events compared with placebo, although hypersensitivity reactions such as urticaria warrant attention [113]. As biologics are used for longer durations and in broader populations, additional rare adverse events may emerge.

Switching between biologics is another safety consideration. Retrospective and real-world studies suggest that switching between omalizumab and dupilumab can be safe and may improve symptom control without increasing adverse event risk [114,115]. However, isolated reports of new adverse effects (e.g., keratoconjunctivitis sicca) after switching highlight that patient factors and underlying disease may influence risk. The absence of a washout period during transition does not appear to increase adverse events in available data, but larger prospective studies are needed.

In summary, biologics for CRSwNP and allergic rhinitis are generally safe and well-tolerated, with mostly mild-to-moderate, self-limiting adverse events. Serious or long-term complications appear uncommon based on current evidence, but continued surveillance is needed as treatment durations extend and broader patient populations are treated. Careful patient selection, regular monitoring, and readiness to adjust therapy are important to maximize benefit and minimize risk.

5.3. Individualized Treatment and Precision Medicine

The management of CRSwNP and allergic rhinitis has evolved from a "one size fits all" approach toward personalized precision medicine. This approach integrates multidimensional assessment (e.g., clinical phenotyping, inflammatory endotyping, and genomic profiling) to select the most appropriate biologic therapy for each patient [116,117]. In CRSwNP, distinguishing eosinophilic from non-eosinophilic disease using tissue or blood biomarkers (e.g., eosinophil counts and cytokine profiles) can influence response to targeted biologics (anti-IL-5, anti-IL-4R, or anti-IgE monoclonal antibodies) [118, 119]. Deep learning models using imaging and histopathology may further improve endotype identification and help allocate treatments more effectively [120, 121]. Individualized therapy aims to maximize clinical benefit while addressing safety and economic concerns associated with long-term use of expensive biologics.

Current evidence supports prioritizing biologics for patients with high-risk features such as frequent recurrence, comorbid asthma, or prominent eosinophilic inflammation. Large-scale clinical studies and real-world data indicate that severe, refractory CRSwNP—particularly type 2 inflammation with coexisting asthma—derives substantial benefit from biologics targeting key inflammatory pathways [122, 123]. Biomarkers such as peripheral blood eosinophils, serum IgE, fractional exhaled nitric oxide (FeNO), and cytokine levels (e.g., IL-5 and IL-13) can help identify likely responders [124, 125]. Integrating clinical features (e.g., nasal polyp score, surgical history, and olfactory dysfunction) with molecular and cellular markers can refine risk stratification and treatment selection [126]. Combining phenotype, endotype, and comorbidity assessment is increasingly recognized as important for optimizing biologic use.

Omics technologies (genomics, transcriptomics, and proteomics) have accelerated progress toward personalized care. High-throughput profiling has identified new biomarkers and molecular signatures describing distinct pathways in CRSwNP and allergic rhinitis [127, 128]. Transcriptomic analyses suggest heterogeneity even within type 2–dominant disease, indicating possible sub-endotypes with different treatment responses [127]. Artificial

intelligence–based analyses of histology and imaging may predict gene expression patterns and spatial heterogeneity, generating digital biomarkers to guide endotype-based decisions [121,129]. To translate these advances into practice, a stepwise roadmap is proposed below. Despite progress, challenges remain, including biomarker validation and standardization, access to cost-effective diagnostics, and the need for robust prospective trials defining optimal selection criteria [130,131]. Disease complexity, including overlapping endotypes and inflammatory pathways, also necessitates flexible treatment algorithms. As data accumulate, integrating clinical, molecular, and digital health information may enable dynamically adaptive pathways based on disease activity and patient needs.

In summary, the shift toward precision medicine in CRSwNP and allergic rhinitis is changing clinical practice. Multidimensional assessment and advanced biomarkers can better match patients to effective biologic therapy, particularly those with high-risk or refractory disease, improving outcomes, quality of life, cost-effectiveness, and safety.

An implementation pathway for multi-omics and AI in routine care may be envisioned in steps. In the near term, multi-omics and AI can be implemented using readily available biomarkers (e.g., blood eosinophils, total IgE, FeNO) and standard clinical indices (NPS, SNOT-22, TNSS) to support treatment eligibility and early response assessment. In the midterm, targeted molecular panels from transcriptomic/proteomic studies could be translated into clinically available assays to refine endotype classification and predict biologic response. In parallel, AI-based tools trained on imaging and digital histopathology could provide automated, reproducible endotype surrogates and reduce inter-observer variability. In the long term, a fully integrated precision workflow could incorporate longitudinal multimodal data (clinical features, molecular signatures, imaging, and real outcomes) into decision-support systems to adjust biologic selection, switching, and discontinuation criteria. Successful translation will require standardization, prospective validation, cost-effectiveness assessment, and integration into multidisciplinary care.

6. Challenges and Future Prospects of Biologics in the Treatment of CRSwNP and AR

6.1. Optimization of Indications and Treatment Pathways

Optimization of indications and treatment pathways for biologics in CRSwNP and allergic rhinosinusitis remains challenging due to a lack of standardized guidelines defining optimal patient populations, initiation timing, and discontinuation criteria [132,133]. Criteria for selecting patients most likely to benefit continue to evolve. Evidence suggests biologics are most appropriate for patients with type 2 inflammation who have failed conventional treatment, such as those with persistent symptoms despite prolonged intranasal corticosteroids, short courses of oral corticosteroids, and/or prior endoscopic sinus surgery [100,134]. However, lack of consensus regarding definitions of "severe" disease complicates decision-making, and real-world data show substantial variability in biologic initiation and discontinuation across practices [135,136], reflecting differences in healthcare systems, patient preferences, and access, and highlighting the need for standardized guidelines.

Questions about when to start and stop biologic therapy are further complicated by disease heterogeneity and variable clinical course. Although randomized controlled trials demonstrate efficacy in severe, refractory disease, no universally accepted algorithm exists for initiation timing, treatment duration, or cessation criteria [137,138]. Some expert consensus documents recommend biologics before surgery in patients with comorbid severe asthma, or in patients for whom surgery is contraindicated or declined [134,139]. Others recommend biologics only after failure of surgery or polyp regrowth within 12 months postoperatively [140]. Discontinuation decisions are often based on symptom control, recurrence risk, and patient preference rather than objective measures, partly due to limited biomarkers predicting response or optimal duration. Another unresolved issue is whether biologics should be used continuously or intermittently. Continuous therapy may provide stable control and reduce early regrowth in severe disease but raises concerns regarding cumulative cost, adherence, and uncertainty about the minimum effective duration for disease modification. Intermittent approaches (planned pauses or retreatment triggered by symptom recurrence, biomarker rises, or endoscopic regrowth) may reduce cost and exposure but could increase risks of rebound inflammation, delayed recognition of relapse, and repeated systemic corticosteroid use. Direct comparative evidence is limited, and discontinuation decisions are often individualized. Future studies should prospectively compare continuous versus intermittent strategies, identify biomarkers predictive of sustained remission or relapse, and establish evidence-based criteria for duration, step-down, and re-initiation.

Multidisciplinary collaboration and evidence-based guidelines are needed to standardize biologic use and maximize outcomes. Collaboration among allergists, otorhinolaryngologists, pulmonologists, and immunologists supports assessment of disease severity, comorbidities, and responses to prior therapies [100,141]. Consensus statements emphasize shared decision-making based on patient preferences, comorbidity profiles, and risk–benefit considerations [139,142]. Standardized care pathways and multidisciplinary case discussions can reduce unwarranted variation. National and international registry data and real-world outcomes can improve algorithms and monitor long-term safety and effectiveness [143,144]. As biologic prescribing increases, collaborative and data-driven approaches will become increasingly important.

Clear indications for initiating and discontinuing biologics also relate to healthcare economics and resource constraints. Biologics are expensive, and widespread prolonged use may burden healthcare systems [145, 146]. Cost-effectiveness studies generally suggest reserving biologics for those most likely to benefit, namely patients with severe, refractory disease who have failed medical and surgical therapies. Regional differences in access and prescribing patterns further support tailored strategies that account for local infrastructure and patient populations [146]. As more real-world data emerge, indications may be refined to ensure clinical appropriateness and economic viability.

6.2. Economic and Accessibility Issues

Cost-effectiveness challenges for biologics depend on healthcare system characteristics, patient populations, and evidence gaps in long-term economic evaluation. Cost-effectiveness is strongly influenced by reimbursement policies, drug pricing, and insurance coverage, and may differ in patients with severe refractory disease, frequent surgical recurrence, or comorbid asthma. Additional economic studies are needed regarding treatment duration, discontinuation strategies, and comparisons between biologics. Cost-effectiveness is also highly contextual and varies between regions.

Biologic therapy for CRSwNP and AR has provided significant advances for patients with severe, refractory symptoms, but high costs remain a major obstacle to widespread use and equitable access. Biologics such as anti-IgE (omalizumab), anti-IL-5 (mepolizumab, reslizumab, benralizumab), and anti-IL-4/IL-13 (dupilumab) show efficacy in randomized trials, but costs are substantially higher than traditional therapies such as intranasal corticosteroids or endoscopic sinus surgery [147,148]. Wholesale costs are high, and prolonged use can burden patients and healthcare systems [145]. Limited reimbursement in many countries further increases out-of-pocket expenses and restricts access.

Cost-effectiveness is therefore a central question. While biologics provide significant improvements for selected severe CRSwNP or AR patients, their high direct costs often make them less cost-effective than established treatments such as functional endoscopic sinus surgery (FESS) for long-term CRSwNP management [149]. FESS may be more economical long term due to lower recurrence and reduced need for ongoing expensive medications [149]. For patients with frequent revision surgeries or multiple comorbidities, biologics may be more cost-effective if they prevent surgery and improve disease control [150]. These findings emphasize the importance of patient selection and the need for real-world economic assessments in different healthcare settings.

Resource allocation and policy considerations are also important. CRSwNP and AR impose large socioeconomic burdens due to prevalence and chronicity [148,151]. Introduction of expensive biologics may increase disparities, particularly in underserved populations with limited access to advanced therapies [13]. Policy reforms (e.g., inclusion in formularies and biosimilar development) may reduce disparities but require cost analyses and negotiations [13]. Lack of harmonized reimbursement leads to variability in access and highlights the need for standardized eligibility criteria and equitable funding.

Access barriers extend beyond pricing and include specialist availability, referral pathways, diagnostic infrastructure (endoscopy, imaging, biomarker testing), and administrative requirements such as prior authorization. Geographic and socioeconomic factors can limit timely evaluation and follow-up in rural or underserved communities. Variation in prescribing practices and health literacy may also contribute to unequal adoption. Addressing disparities may require guideline-based eligibility criteria, expanded reimbursement for high-need patients, value-based pricing or national negotiations, and adoption of biosimilars and patient assistance programs. Multidisciplinary shared-care models and telemedicine follow-up may extend specialist expertise to regions with limited access. Equity metrics should also be incorporated into trials and registries to ensure future evidence benefits diverse

populations.

To address these challenges, cost–benefit analyses should consider indirect costs such as productivity loss and quality-of-life improvement, in addition to direct costs [149]. Ongoing studies on dose optimization, identification of patients most likely to benefit, and use of digital health tools for remote monitoring may further improve economic value [13, 91]. Over time, biosimilars and precision medicine approaches may improve affordability and accessibility.

In summary, although biologics are promising for CRSwNP and AR, high cost and limited reimbursement remain major barriers. Addressing these issues will require economic evaluation, resource optimization, and policy initiatives to expand access for eligible patients.

6.3. Future Research Directions

Future biologic therapy for CRSwNP and allergic rhinitis will continue to evolve as research identifies new targets and optimizes combination strategies. There remains a need to treat patients who do not respond to type 2 inflammation–targeted agents or who have mixed or non–type 2 endotypes [34, 152]. Agents targeting upstream mediators such as TSLP (e.g., tezepelumab) may provide options for corticosteroid-refractory or biologic-insensitive disease, as suggested by reductions in nasal polyp score and symptom burden in recent phase 3 trials [71]. Broadening the therapeutic field to include agents acting on different inflammatory axes may help address heterogeneity in CRSwNP and allergic rhinitis. Future regimens may include combination biologics or sequential therapies tailored to specific endotypes and comorbidities, potentially improving disease control compared with monotherapy.

Another priority is the evaluation of long-term safety and effectiveness in real-world settings. While trials support short- to medium-term safety and tolerability, fewer data exist on long-term safety, durability of response, and impacts on healthcare resources [99, 153]. Real-world data can clarify rare adverse events, adherence patterns, disease modification potential, and cost-effectiveness in different populations [154]. Clinical heterogeneity underscores the need for reliable biomarkers predicting treatment success and long-term outcomes. Baseline blood eosinophils and total serum IgE have been proposed as predictors of response to dupilumab but require validation in larger and more diverse cohorts with longer follow-up [153]. Health systems must also address disparities in access and prescribing patterns noted in regional analyses [144].

Multi-omics technologies (proteomics, transcriptomics, genomics) may further advance personalized medicine in CRSwNP and allergic rhinitis. High-throughput profiling can identify new subtypes, reveal mechanisms of response and resistance, and uncover therapeutic targets beyond type 2 inflammation [155,156]. Transcriptomic and proteomic analyses have identified distinct endotypes with different inflammatory signatures and potential differential responses to specific biologics [155]. As these technologies become more accessible, patient stratification may become more precise, enabling truly individualized treatment based on molecular and clinical characteristics and informing rational design of combination therapies targeting complementary pathways.

In summary, future research should focus on novel targets and combination/sequence strategies, the generation of robust long-term real-world evidence, and multi-omics approaches to precision medicine. These directions will help overcome current limitations, optimize outcomes, and ensure advances in biologic therapy benefit diverse patient populations affected by CRSwNP and allergic rhinitis.

7. Conclusion

In summary, the advent of biologics has marked a major breakthrough in the treatment of difficult-to-treat and recurrent chronic rhinosinusitis with nasal polyps (CRSwNP) and allergic rhinitis. From a clinical perspective, monoclonal antibodies targeting IgE, IL-5, and the IL-4/IL-13 pathways have demonstrated promising efficacy and favorable safety profiles across different patient populations and endotypes. These targeted therapies not only alleviate disease symptoms but also significantly improve patients' quality of life.

However, the rapidly evolving evidence base for biologic therapies necessitates a balanced and critical approach. While current studies confirm the therapeutic potential of biologics, heterogeneous treatment responses highlight the need for improved biomarker-driven patient selection. Tailoring therapy based on precise immunological and clinical phenotyping may help maximize therapeutic benefit while minimizing unnecessary exposure

and healthcare costs. In addition, standardized and validated measures for treatment response and long-term safety monitoring are required to ensure sustained effectiveness and to identify potential adverse effects during prolonged use.

Future research and clinical practice should focus on advancing precision medicine in rhinology, including the integration of molecular diagnostics and real-world data to optimize treatment algorithms. Such approaches will enable clinicians to deliver the right biologic to the right patient at the right time. Equally important are pragmatic considerations, such as cost-effectiveness, drug accessibility, and multidisciplinary collaboration among allergists, otolaryngologists, and immunologists, to ensure that biologics become equitable and effective components of routine clinical care.

In conclusion, biologic therapies represent an important and promising treatment option for refractory CRSwNP and allergic rhinitis, particularly in cases where conventional therapies have failed. Nevertheless, their full potential can only be realized through continued efforts to refine patient selection, monitor long-term outcomes, and address implementation challenges. By integrating emerging scientific evidence with clinical experience, biologics are poised to support a new era of personalized, mechanism-based therapy aimed at improving outcomes and quality of life in patients with nasal inflammatory diseases.

Author Contributions

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