Immunotherapy in Chronic Rhinosinusitis: Current Perspectives

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Abstract:

Background: Chronic rhinosinusitis (CRS) is a heterogeneous inflammatory disease of the upper airways that affects approximately 10–12% of the population and imposes a substantial clinical and socioeconomic burden. A considerable proportion of patients – particularly those with chronic rhinosinusitis with nasal polyps (CRSwNP) – exhibit persistent symptoms and frequent recurrences despite optimal conventional therapy, including intranasal corticosteroids, systemic corticosteroids, antibiotics, and functional endoscopic sinus surgery. Advances in endotype-driven research have identified type 2 (T2) inflammation, characterized by eosinophilia, elevated IgE, and activation of IL-4, IL-5, and IL-13 pathways, as a central mechanism underlying disease severity and treatment resistance.

Objective: This narrative review aims to synthesize current evidence on immunotherapeutic strategies in CRS, with particular emphasis on biologic therapies, and to evaluate their mechanisms of action, clinical efficacy, safety profiles, and role in personalized disease management.

Methods: A comprehensive review of the contemporary literature was conducted, focusing on randomized controlled trials, real-world observational studies, and international guideline recommendations addressing allergen immunotherapy (AIT) and biologic agents targeting key mediators of T2 inflammation.

Results: AIT remains the only disease-modifying treatment for patients with allergic CRS, demonstrating sustained symptom reduction and improved postoperative outcomes in appropriately selected individuals. Biologic therapies have fundamentally transformed the management of moderate-to-severe, uncontrolled CRSwNP. Agents targeting IL-4/IL-13 (dupilumab), IL-5 or its receptor (mepolizumab, benralizumab), IgE (omalizumab), and upstream epithelial alarmins such as thymic stromal lymphopoietin (tezepelumab) consistently reduce nasal polyp burden, improve sinonasal symptoms and olfactory function, decrease reliance on systemic corticosteroids, and lower the need for revision surgery. These therapies show favorable safety and tolerability profiles and provide clinically meaningful benefits across a broad spectrum of T2-driven endotypes.

Conclusions: Immunotherapy has emerged as a cornerstone of modern CRS management, enabling a shift from symptom-based treatment toward targeted, mechanism-driven interventions. Biologic therapies offer substantial benefits for patients with severe or refractory CRSwNP and represent a major advance toward precision medicine. Future priorities include refinement of predictive biomarkers, optimization of biologic selection and sequencing, and integration of immunotherapy into individualized, endotype-guided treatment algorithms.

INTRODUCTION

Chronic rhinosinusitis is a multifactorial inflammatory disorder characterized by marked heterogeneity in clinical presentation, immunopathology, and treatment response. CRS is classically divided into chronic rhinosinusitis with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP), each associated with distinct inflammatory profiles [1,2]. Contemporary endotyping has demonstrated that T2 inflammation – driven by eosinophils, IgE, and cytokines such as IL-4, IL-5, and IL-13 – is predominant in CRSwNP and accounts for treatment resistance and high recurrence rates following surgery [3].

These insights have shifted management paradigms toward personalized medicine, with immunotherapy becoming a central component of care, particularly for patients with severe or refractory disease [4, 5].

1. Pathophysiology of Chronic Rhinosinusitis

CRS involves dysregulation of both innate and adaptive immune responses. In CRSwNP, T2 inflammation leads to epithelial barrier dysfunction, impaired mucociliary clearance, tissue remodeling, and polyp formation through sustained activation of IL-4/IL-13 and IL-5 pathways [3, 6]. Eosinophilic infiltration and local IgE production perpetuate chronic inflammation and corticosteroid dependence.

In contrast, CRSsNP is more commonly associated with non-T2 inflammation, characterized by neutrophilic responses, microbial dysbiosis, and epithelial damage. Increasing evidence also highlights the role of epithelial-derived cytokines („alarmins") such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 in initiating and amplifying T2 inflammation, thereby bridging innate and adaptive immune pathways [7].

2.Allergen Immunotherapy

Allergen immunotherapy (AIT) remains the only disease-modifying treatment for patients with allergic rhinitis and allergy-associated CRS. Delivered as subcutaneous (SCIT) or sublingual immunotherapy (SLIT), AIT induces immune tolerance by enhancing regulatory T-cell responses, suppressing Th2 activity, reducing IgE production, and increasing protective IgG4 antibodies [8].

Clinical studies demonstrate that AIT reduces symptom severity, decreases corticosteroid requirements, improves surgical outcomes, and contributes to long-term disease stabilization in patients with allergic CRS. However, its efficacy is limited in non-atopic CRSwNP, underscoring the importance of accurate patient selection [5, 9].

3.Biologic Therapies

Biologic therapies represent the most significant therapeutic advance in the management of moderate-to-severe, uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP) driven by type 2 (T2) inflammation, particularly in patients with recurrent disease after surgery, systemic corticosteroid dependence, and/or comorbid asthma or NSAID-exacerbated respiratory disease (N-ERD). Current clinical practice increasingly emphasizes biologic selection based on disease severity, comorbidities, and inflammatory characteristics, including blood eosinophil counts, total IgE levels, and validated clinical indices such as nasal polyp score (NPS) and SNOT-22. However, no single biomarker reliably predicts therapeutic response across all biologic agents, underscoring the need for individualized treatment strategies [10, 11].

3.1. Dupilumab (anti–IL-4Rα; IL-4/IL-13 pathway inhibition)

Dupilumab is the most extensively studied biologic therapy for CRSwNP and has demonstrated consistent efficacy across randomized controlled trials and real-world clinical settings. In addition to significant reductions in nasal polyp burden, nasal congestion, and olfactory dysfunction, dupilumab has been shown to decrease the need for systemic corticosteroids and revision sinus surgery [3, 4].

Real-world observational studies further support these findings, demonstrating durable symptom control, improved quality of life, and favorable treatment persistence in patients with severe, refractory disease, including those with prior multiple surgical interventions and coexisting asthma. Emerging comparative effectiveness analyses suggest that dupilumab provides broad clinical benefit across multiple T2-driven pathways, supporting its use as a first-line biologic option in many patients with CRSwNP [12–14].

3.2. Anti–IL-5 and anti–IL-5 receptor therapies

Agents targeting the IL-5 pathway, including mepolizumab (anti–IL-5) and benralizumab (anti–IL-5 receptor), are particularly effective in patients with eosinophil-dominant CRS endotypes. Clinical trials and real-world studies demonstrate reductions in tissue and peripheral eosinophilia, improvements in endoscopic scores, and clinically meaningful symptom relief [6, 15].

Recent observational data indicate that mepolizumab may also be beneficial in selected CRSwNP patients without severe asthma, expanding its potential applicability beyond traditional asthma-driven indications. In addition, newer long-acting IL-5–targeting biologics with extended dosing intervals have demonstrated efficacy in reducing nasal polyp size and disease burden, potentially improving treatment adherence and patient convenience [16, 17].

3.3. Omalizumab (anti-IgE)

Omalizumab is particularly effective in CRSwNP patients with atopic disease, elevated serum IgE, and concomitant allergic asthma. Clinical studies have demonstrated significant improvements in nasal symptoms, polyp size, and health-related quality of life. Real-world evidence confirms

these benefits in routine practice and highlights omalizumab as a valuable option in patients with IgE-driven disease biology [7, 12, 16].

In clinical decision-making, omalizumab is often favored when allergic comorbidity predominates, although overlapping inflammatory mechanisms frequently necessitate a multifactorial approach to biologic selection.

3.4. Tezepelumab (anti-TSLP): targeting upstream epithelial inflammation

Blockade of thymic stromal lymphopoietin (TSLP), an upstream epithelial „alarmin," represents an important expansion of biologic strategies in CRSwNP. Clinical trials evaluating tezepelumab have demonstrated significant reductions in nasal polyp size, nasal obstruction, and overall symptom burden in patients with severe, uncontrolled disease. Importantly, treatment has also been associated with reduced need for systemic corticosteroids and surgical intervention.

By targeting an upstream mediator of T2 inflammation, TSLP inhibition offers a mechanistically distinct approach that may benefit patients with complex or refractory disease, including those with partial or inadequate responses to downstream cytokine blockade [18–20].

Table 1. Comparative overview of biologic therapies in chronic rhinosinusitis with nasal polyps (CRSwNP)

Biologic agent	Molecular target	Predominant inflammatory endotype	Key clinical indications
Dupilumab	IL-4 receptor α (blocks IL-4 and IL-13 signaling)	Broad type 2 (T2) inflammation	Moderate-to-severe CRSwNP; steroid-dependent disease; recurrent nasal polyps after surgery; comorbid asthma
Mepolizumab	Interleukin-5 (IL-5)	Eosinophilic T2 endotype	CRSwNP with blood or tissue eosinophilia; comorbid eosinophilic asthma; NSAID-exacerbated respiratory disease
Benralizumab	IL-5 receptor α	Eosinophilic T2 endotype	Severe eosinophilic CRSwNP; asthma-dominant phenotype; patients with marked eosinophilia
Omalizumab	Immunoglobulin E (IgE)	IgE-driven T2 inflammation	CRSwNP with atopy; elevated serum IgE; allergic asthma or allergic rhinitis
Tezepelumab	Thymic stromal lymphopoietin (TSLP)	Upstream T2 activation (alarmin-driven)	Severe, uncontrolled CRSwNP; refractory disease; mixed or complex inflammatory endotypes

3.5. Clinical implications and future directions

As the biologic armamentarium for CRSwNP continues to expand, recent literature increasingly emphasizes practical considerations relevant to routine clinical care:

- Real-world effectiveness and treatment persistence, which are critical for translating trial efficacy into sustained disease control [12, 21].
- Biologic sequencing and switching strategies, particularly in patients with overlapping endotypes, comorbid asthma, or suboptimal response to initial therapy [14, 16].
- The unmet need for validated predictive biomarkers, which remains a major barrier to fully personalized biologic therapy and is a key focus of ongoing research [10, 11].

4. Safety Considerations

Both AIT and biologic therapies demonstrate favorable safety profiles. AIT is associated mainly with local reactions, while biologics are generally well tolerated, with mild injection-site reactions and transient eosinophilia being the most commonly reported adverse events. Long-term data support sustained safety and tolerability across biologic agents [3,4,9].

Conclusion

Immunotherapy has become a cornerstone in the management of chronic rhinosinusitis, particularly in patients with T2-driven inflammation and CRSwNP. Biologic therapies – especially dupilumab – have redefined treatment goals by enabling sustained disease control and reducing reliance on systemic corticosteroids and surgery. Future progress will depend on improved biomarker-driven patient selection, optimized sequencing strategies, and integration of emerging biologic targets into personalized treatment algorithms.

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