

The Evolving Role of Biologics in Otorhinolaryngology: Innovations, Applications, and Future Perspectives

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ABSTRACT

The introduction of biologics into otorhinolaryngology has marked a significant shift in the management of complex and chronic ENT (Ear, Nose and Throat) conditions. This review delves into the mechanisms, clinical applications, and evidence supporting the use of biologics in treating disorders such as chronic rhinosinusitis, allergic rhinitis, head and neck cancer, and autoimmune inner ear disease. By examining current research and clinical trials, this article provides an in-depth analysis of the transformative impact of biologics and discusses future directions in this rapidly advancing field.

KEY WORDS

Biologics, chronic rhinosinusitis, Ear, Nose and Throat

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INTRODUCTION

The advent of biologics represents a significant shift in the management of complex ENT conditions, which traditionally relied on surgical interventions and pharmacological therapies. Biologics-therapeutic agents derived from biological sources-introduce novel treatment strategies for chronic and refractory conditions previously difficult to manage. These agents, including monoclonal antibodies, cytokine inhibitors, and fusion proteins, offer targeted therapeutic approaches with the potential for superior efficacy and reduced side effects compared to conventional treatments.^{1,2}

Mechanisms of Biologics

Biologics are designed to precisely modulate immune and inflammatory responses. Their mechanisms of action include:

- 1. Monoclonal Antibodies:** Engineered to bind specifically to antigens such as cytokines or cell surface receptors, monoclonal antibodies inhibit pathological interactions and inflammatory pathways. For instance, monoclonal antibodies targeting IL-5 or IL-4 receptors can effectively reduce eosinophilic inflammation in chronic rhinosinusitis and allergic rhinitis.^{2,3}
- 2. Cytokine Inhibitors:** These biologics block key cytokines involved in inflammatory processes. Inhibitors of interleukins (e.g., IL-5, IL-4) and tumor necrosis factor-alpha (TNF- α) have shown efficacy in managing various ENT conditions by reducing inflammation and modulating immune responses.¹
- 3. Receptor Antagonists:** Fusion proteins and receptor antagonists interfere with cellular signaling pathways by

binding to specific receptors, thus preventing the activation of inflammatory pathways. This targeted approach helps mitigate unwanted immune responses.⁴

4. Fusion Proteins: These combine different biological components to simultaneously target multiple aspects of a disease process. For example, fusion proteins that combine cytokine receptors with immunoglobulin domains can block cytokine signaling and reduce inflammation.⁵

Applications in Otorhinolaryngology

Biologics have demonstrated significant benefits in treating various otorhinolaryngological conditions, particularly those characterized by chronic inflammation and immune dysregulation. Key applications include:

1. Chronic Rhinosinusitis (CRS)

Chronic rhinosinusitis, especially with nasal polyps, is a condition marked by prolonged inflammation and mucosal thickening, leading to substantial morbidity. Traditional treatments have included nasal corticosteroids and surgery; however, biologics have emerged as promising alternatives.

- **Mepolizumab:** Mepolizumab is a humanized anti-IL-5 monoclonal antibody that prevents the binding of IL-5 to its receptor on eosinophil granulocytes, mast cells, and other target cells and selectively inhibits eosinophilic inflammation, thus significantly reduces polyp size and improves nasal congestion and overall symptoms and improve quality of life in patients with severe CRS.²
- **Dupilumab:** This biologic inhibits IL-4 and IL-13 signaling by targeting the IL-4 receptor alpha subunit. Studies have shown that dupilumab reduces nasal polyp size, improves symptom scores, and enhances quality of life for patients with CRS with nasal polyps. Dupilumab's effectiveness was demonstrated in the pivotal studies such as the SINUS-24 and SINUS-52 trials, which reported significant clinical benefits and safety profiles.¹

2. Allergic Rhinitis

Allergic rhinitis, characterized by inflammation of the nasal mucosa in response to allergens, can be difficult to manage with conventional therapies alone. Biologics have provided new treatment options, particularly targeting IgE.

- **Omalizumab:** An anti-IgE monoclonal antibody that decreases free IgE levels, reducing the severity of allergic reactions. Clinical trials have shown that omalizumab is effective in alleviating nasal symptoms and reducing the need for other medications.³ The drug's efficacy in allergic rhinitis has been well-documented in various studies, showing significant improvements in patient-reported outcomes and quality of life.

3. Head and Neck Cancer

Biologics have also made strides in the management of head and neck cancer, particularly in enhancing the

efficacy of traditional therapies and offering new treatment modalities.

- **Cetuximab:** This anti-EGFR (epidermal growth factor receptor) monoclonal antibody is used in treating head and neck squamous cell carcinoma (HNSCC). Cetuximab has been shown to improve survival rates when combined with chemotherapy or radiation therapy.⁶ Its role in targeted therapy for HNSCC has been validated in several clinical trials, demonstrating its impact on tumor response and patient outcomes.

- **Pembrolizumab and Nivolumab:** These immune checkpoint inhibitors target PD (programmed cell death protein)-1, a protein that inhibits immune responses. They have demonstrated efficacy in treating recurrent or metastatic HNSCC by reactivating the immune system to target cancer cells. Trials such as CHECKMATE 141 have shown that these agents can significantly improve overall survival compared to standard chemotherapy regimens.⁶

4. Autoimmune Inner Ear Disease (AIED)

AIED, characterized by progressive hearing loss due to autoimmune processes, represents a challenging therapeutic area. Biologics targeting specific autoimmune mechanisms offer potential new treatments.

- **Rituximab:** An anti-CD20 monoclonal antibody that depletes B-cells, has been used off-label for AIED with encouraging results in some studies. Rituximab's impact on AIED has been explored in various case series and studies, suggesting potential benefits in stabilizing or improving hearing loss associated with autoimmune inner ear conditions.⁷

5. Tympanic Membrane Regeneration

Traditionally addressed through surgical techniques, recent advancements in growth factor therapies offer a promising alternative.

- **EGF and b-FGF:** Human-derived growth factors, including Epidermal Growth Factor (EGF) and Basic Fibroblast Growth Factor (b-FGF), have been explored for tympanic membrane perforations. Recent meta-analyses indicate that b-FGF notably enhances closure rates, while heparin-binding epidermal growth factor-like growth factor has shown superior efficacy in promoting membrane healing.^{8,9}

6. Sensorineural Hearing Loss

Current research focuses on innovative approaches, including otoprotection, hair cell regeneration, tinnitus reduction, balance improvement, and central hearing disorder management. Emerging treatments involve novel and repurposed medications, gene therapy using RNA interference, and stem cell therapies.¹⁰

Clinical Evidence and Trials

A number of clinical trials have provided evidence for the efficacy of biologics in otorhinolaryngology. Notable trials include:

- **SINUS-24 and SINUS-52 Trials:** These studies evaluated dupilumab in patients with CRS with nasal polyps, demonstrating significant reductions in polyp size and improvements in symptoms and quality of life.¹ Dupilumab was found to be effective in alleviating nasal congestion and enhancing patient-reported outcomes.

- **CHECKMATE 141:** A pivotal trial evaluating nivolumab in recurrent or metastatic HNSCC demonstrated improved overall survival compared to standard chemotherapy. This study underscores the potential of immune checkpoint inhibitors in extending survival for patients with advanced head and neck cancer.⁶

Challenges and Considerations

Despite their benefits, the use of biologics in otorhinolaryngology presents several challenges:

1. **Cost:** Biologics are often costly, which can limit their accessibility for some patients. The high cost of these therapies necessitates careful consideration of their economic impact and cost-effectiveness in clinical practice.¹¹

2. **Side Effects:** While generally well-tolerated, biologics can cause adverse effects, including infections, allergic reactions, and long-term risks. Monitoring and managing these potential side effects are crucial for optimizing patient safety.¹²

3. **Long-Term Data:** Long-term efficacy and safety data for many biologics are still evolving. Continued research is needed to fully understand the long-term impacts of biologics on patient outcomes and potential risks.¹³

4. **Individual Variability:** The response to biologics can vary among patients based on genetic factors, comorbid conditions, and other variables. Personalized treatment approaches are essential to maximize the benefits of biologics and minimize adverse effects.¹⁴

Future Directions

The future of biologics in otorhinolaryngology holds several exciting prospects:

1. **Emerging Therapies:** New biologics targeting additional cytokines, immune pathways, and cellular processes are under development.¹⁵ These therapies may expand the range of treatment options available for various ENT conditions and offer improved efficacy and safety profiles.

2. **Combination Therapies:** Combining biologics with other therapeutic modalities, such as conventional drugs or novel small molecules, may enhance treatment outcomes and reduce the risk of resistance. Research into combination therapies could provide more effective treatment strategies for complex conditions.

3. **Personalized Medicine:** Advances in genomics and personalized medicine may enable more precise targeting of biologics based on individual patient profiles. Tailoring treatments to genetic and phenotypic characteristics could improve outcomes and minimize side effects.

4. **Expanded Indications:** Ongoing research may identify new indications for existing biologics, broadening their application in otorhinolaryngology. Exploring novel uses and combinations of biologics could further enhance their role in managing ENT disorders.

CONCLUSION

Biologics have significantly advanced the management of otorhinolaryngological conditions, offering targeted and effective treatments for chronic and complex diseases. As research progresses and new therapies emerge, biologics are poised to play an increasingly critical role in ENT practice. The integration of these therapies promises to enhance patient outcomes, though careful consideration of cost, safety, and individual variability remains essential. Continued innovation and research will likely drive further advancements in the use of biologics in otorhinolaryngology.

REFERENCES

1. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. 2019 Nov 2;394(10209):1638-50.
2. Bachert C, Sousa AR, Han JK, Schlosser RJ, Sowerby LJ, Hopkins C, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps: Treatment efficacy by comorbidity and blood eosinophil count. *J Allergy Clin Immunol*. 2022 May;149(5):1711-21.
3. Tsabouri S, Ntritsos G, Koskeridis F, Evangelou E, Olsson P, Kostikas K. Omalizumab for the treatment of allergic rhinitis: a systematic review and meta-analysis. *Rhinology*. 2021 Dec 1;59(6):501-10.
4. Armstrong AW, Papp K, Kircik L. Secukinumab: Review of Clinical Evidence from the Pivotal Studies ERASURE, FIXTURE, and CLEAR. *J Clin Aesthet Dermatol*. 2016 Jun;9(6 Suppl 1):S7-S12. Epub 2016 Jun 1.
5. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med*. 1999 Mar 16;130(6):478-86.
6. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med*. 2016 Nov 10;375(19):1856-67.
7. Balouch B, Meehan R, Suresh A, Zaheer HA, Jabir AR, Qatanani AM et al. Use of biologics for treatment of autoimmune inner ear disease. *Am J Otolaryngol*. 2022 Sep-Oct;43(5):1035-76.
8. Jackler RK. A regenerative method of tympanic membrane repair could be the greatest advance in otology since the cochlear implant. *Otol Neurotol*. 2012; 33(3):289.
9. Santa Maria PL, Gottlieb P, Santa Maria C, Kim S, Puria S, Yang YP. Functional Outcomes of Heparin-Binding Epidermal Growth Factor-Like Growth Factor for Regeneration of Chronic Tympanic Membrane Perforations in Mice. *Tissue Eng Part A*. 2017 May;23(9-10):436-44.

10. Amariutei AE, Jeng JY, Safieddine S, Marcotti W. Recent advances and future challenges in gene therapy for hearing loss. *R Soc Open Sci*. 2023 Jun 14;10(6):230644.
11. Huoponen S, Blom M. A systematic review of the cost-effectiveness of biologics for the treatment of inflammatory bowel diseases. *PLoS one*. 2015 Dec 16;10(12):e0145087.
12. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev*. 2011 Feb 16;2011(2):CD008794.
13. Ayen-Rodríguez A, Pereyra-Rodríguez JJ, Navarro-Triviño FJ, Alcantara-Luna S, Domínguez-Cruz J, Galán-Gutiérrez M, et al. Long-Term Effectiveness and Safety of Biologic and Small Molecule Drugs for Moderate to Severe Atopic Dermatitis: A Systematic Review. *Life (Basel)*. 2022 Jul 30;12(8):1159.
14. Membrive Jiménez C, Pérez Ramírez C, Sánchez Martín A, Vieira Maroun S, Arias Santiago SA, Ramírez Tortosa MDC, et al. Influence of Genetic Polymorphisms on Response to Biologics in Moderate-to-Severe Psoriasis. *J Pers Med*. 2021 Apr 12;11(4):293.
15. Drug Bank. Biologics: Innovations, challenges, and the road ahead. Drug Bank. Published 2022 [date not provided]. Accessed 2024 Aug 8. Available from: <https://blog.drugbank.com/biologics-innovations-challenges-and-the-road-ahead/>