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Role of Interleukin 5 Inhibition in the Treatment of Eosinophilic Otitis Media

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Abstract

Objective. Eosinophilic otitis media (EOM) is a rare form of middle ear disease characterized by a viscous effusion rich in eosinophils, a resistance to conventional treatments, and an association with bronchial asthma. The relationship between asthma and EOM suggests similarities in pathogenesis and treatment possibilities. Recent biologic therapies, specifically those that target interleukin 5 (IL-5), have demonstrated efficacy in controlling eosinophil-driven asthma, yet their impact on the treatment of pathologically similar diseases remains unmeasured. This study identifies patients who have EOM, reviews their otologic clinical course, and investigates the impact of anti-IL-5 drugs on chronic ear disease.

Study Design. Retrospective chart review.

Setting. University of Florida Health, an academic medical center.

Methods. A review of 120 patients treated with benralizumab or mepolizumab was performed. Imaging evidence of otomastoiditis was used to identify 9 patients with possible EOM. Two patients were treated with benralizumab, and the remaining 7 received mepolizumab injections.

Results. After starting treatment, 5 patients had complete resolution of middle ear effusions (3 with mepolizumab and 2 with benralizumab); 1 had stable middle ear effusion; and 1 patient's disease status could not be determined due to a lack of follow-up. The remaining 2 patients did not have effusions at the time when anti-IL-5 therapy was initiated, and they have not relapsed since starting treatment.

Conclusion. EOM is a rare disease that otolaryngologists should include in their differential diagnosis, especially in refractory cases. Anti-IL-5 agents show efficacy in treating EOM, and prospective multicenter clinical trials are needed to further characterize the effect of anti-IL-5 therapies.

Keywords

eosinophilic otitis media, chronic otitis media, biologic therapy

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Chronic otitis media describes a diverse spectrum of pathologic conditions that result in persistent inflammation of the middle ear and mastoid cavity. Although the management of chronic otitis media can vary, classification of disease patterns can aid in choosing the most appropriate and definitive treatment modality.

First described by Tomioka et al, eosinophilic otitis media (EOM) is considered a recalcitrant form of chronic otitis media.[1] Patients with EOM often undergo many of the traditional treatments for otitis media, including antibiotics, steroids, myringotomy, tympanostomy tube placement, and tympanomastoidectomy, with little relief in symptoms. Further disease-defining characteristics include highly viscous eosinophilic effusion as well an association with bronchial asthma and nasal polyposis.[2-4]

The close clinical relationship between asthma and EOM suggests similarities in pathogenesis. At the cellular level, an asthmatic bronchospasm begins with the inhalation of foreign antigens, which triggers a complex inflammatory process. This inflammation stimulates the production of several chemical mediators, including IgE antibodies interleukin 4 (IL-4) and interleukin 5 (IL-5).[5] Given its crucial role in eosinophil activation, IL-5 has become an important molecular target for new pharmacologic therapies in the treatment of asthma. Several biologic drugs, such as mepolizumab and reslizumab (anti-IL-5 antibodies) as well as benralizumab (an anti-IL-5 receptor antibody), have demonstrated efficacy in reducing the frequency of asthma exacerbations.[6-8]

Currently, there are many publications that investigate the role of anti-IL-5 drugs in the treatment of asthma and chronic rhinosinusitis with nasal polyposis.[9] By comparison, there is a paucity of literature studying the role of these new

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Table 1. Treatment Outcomes in Patients Receiving Anti-IL-5 Therapy. [a]

			Effusion [b]		Eosinophils [c]		Audiology [d]		
Patient	Drug	No. of injections	Before	After	Before	After	Before	After	Side effects
1	Mepolizumab	30	Yes	No	80		Moderate, conductive	Mild-moderate, conductive	None
2	Benralizumab	8	Yes	No	600	0			None
3	Mepolizumab	27	Yes	Yes	1141	0			None
4	Mepolizumab	6	No	No	391		Moderate SNHL		None
5	Mepolizumab	21	Yes	No	454	100	Moderate SNHL		Fatigue, myalgias
6	Mepolizumab	12	Yes	No	657		Moderate, conductive	Mild, conductive	None
7	Mepolizumab	Unclear	Yes	Yes	370	0			None
8	Benralizumab	8	Yes	No	200	0	Moderate, conductive	Moderate, conductive	None
9	Mepolizumab	15	No	No	1137				None

Abbreviation: SNHL, sensorineural hearing loss.
[a]Blank cells indicate *not applicable*.
[b]Presence of middle ear effusion before and after starting anti-IL-5 therapy.
[c]Absolute number of eosinophils present in serum before and after starting anti-IL-5 therapy.
[d]Hearing loss based on audiologic results before and after starting anti-IL-5 therapy.

biologics in the treatment of EOM. Given the significant burden of eosinophils in EOM and its close relationship with asthma, we hypothesize that IL-5-directed therapies will assist in the treatment.

Methods

A retrospective chart review was performed on all patients treated with IL-5-directed therapies between January 2008 and September 2019 at the University of Florida. This minimal-risk retrospective study received approval by the University of Florida Institutional Review Board before initiation. Patients aged <18 years were excluded. Patients were assessed for history of acute otitis media, chronic otitis media with effusion, otologic surgery, and hearing loss. Pertinent imaging was reviewed with audiologic and pulmonary function testing, as well as any history of allergic or chronic rhinosinusitis. Of the 120 patients treated with biologics, 9 demonstrated evidence of chronic middle ear disease. Data were collected on these 9 patients, focusing on the presence of middle ear effusion, audiologic measures, and serum eosinophil levels.

Results

Results are outlined in **Table 1**. Of the 9 patients identified with a history of middle ear disease, the majority were female (80%) and Caucasian (70%). All 9 patients were prescribed anti-IL-5 therapy for severe eosinophilic asthma. Eight patients had serum-proven eosinophilia, and 1 had biopsy-proven eosinophilia. Each patient had a documented history of chronic rhinosinusitis, and 8 had a documented history of nasal polyposis. The mean (SD) age at administration of biologics was 56.6 (13.4) years. Seven patients were treated with mepolizumab, and 2 received benralizumab injections. The mean duration of treatment was 17.1 (8) months at the time when the study was conducted. The drugs were well tolerated among all 9 patients, and side effects were mild and self-limiting. The primary outcome measure of this study was resolution of middle ear effusion. Secondary measures included audiometric improvement and adequate suppression of eosinophil levels.

Effusions

Seven patients had middle ear effusions before starting treatment with IL-5 inhibitors. Five of the 7 experienced complete resolution. Two were treated with benralizumab and 3 with mepolizumab. One patient was lost to follow-up, and 1 patient's effusion was unchanged since starting biologics. Two patients had middle ear effusions that cleared before the initiation of biologic therapy. Neither patient has demonstrated recurrence of middle ear disease since starting biologics.

Eosinophils

Serum eosinophil levels were elevated in 7 of 9 patients before starting treatment with IL-5-directed therapy. Of the 5 patients whose eosinophil levels were measured after starting therapy, 4 were below detectable levels. The other patient's eosinophil levels decreased to within normal limits.

Audiology

Five patients underwent audiologic testing before the initiation of anti-IL-5 therapy. Posttreatment audiometry was available in 3 patients. All 3 demonstrated an improvement in hearing. Two patients (Nos. 4 and 5) reported subjective hearing improvements after starting therapy; however, there are no posttreatment audiologic data. One patient (No. 8) reported subjective deterioration in hearing after discontinuing anti-IL-5 therapy.

Discussion

The diagnosis of EOM requires the recognition of otologic symptoms and coexisting eosinophil-driven diseases. Iino et

al proposed a set of diagnostic criteria that include histologic visualization of eosinophil-dominant middle ear effusion with $\geq$2 of the following: viscous effusion, resistance to conventional treatment, and an association with nasal polyposis, chronic rhinosinusitis, or bronchial asthma.[2,10] Definitive diagnosis requires global evaluation of the patient.

Of the 120 patients treated with IL-5-directed therapy, 9 demonstrated clinical or radiographic evidence of chronic middle ear disease suggestive of EOM. These data suggest that EOM is likely an underrecognized disease. Patients with nasal polyposis and bronchial asthma should be screened for coexisting otologic symptoms.

There was complete resolution of middle ear effusions in 5 of 7 patients treated with IL-5-directed therapy. This occurred an average of 4.4 (2.3) months after therapy initiation. One of the 5 patients took a course of steroids during the study period. However, this patient's effusion cleared before starting steroids. Two of the 5 patients received antibiotics during the study period: 1 took a 10-day course of amoxicillin before the clearance of her effusion, and 1 took a 7-day course of cephalexin after her effusion had already cleared. None of these patients received tympanostomy tubes. The middle ear effusion for patient 8 cleared 5 months after starting benralizumab, though it recurred 2 months after stopping biologic therapy. The other 4 patients who had improvement in middle ear effusions while on therapy demonstrated no evidence of recurrence while biologics were continued. These data suggest that IL-5 inhibitors may prove effective in the treatment and prevention of middle ear effusions, particularly in those with eosinophil-driven diseases. We suspect that, given the recalcitrant nature of EOM, biologics should be continued even in the absence of otologic symptoms to prevent recurrence.

Audiometric data were limited in this review. Five patients underwent audiometry before starting anti-IL-5 therapy: 1 patient was referred to otolaryngology for aural fullness, 2 for subjective hearing loss, 1 for tinnitus and vertigo, and 1 for vertigo. Two of the 4 patients who did not have audiograms were seen by the otolaryngology department for tinnitus, and the remaining 2 patients were not. Of the 5 patients who received audiograms, 3 had conductive hearing loss while the remaining 2 had mixed hearing loss. Posttreatment audiometry was available in 3 patients who demonstrated air-bone gap closure after starting treatment. These data suggest that patients with EOM-induced conductive hearing loss may experience improvement with IL-5 inhibitors. Sensorineural hearing loss is also common in patients with EOM: the etiology is unknown, but it is hypothesized that eosinophils enter the inner ear through the round window, causing direct cochlear damage.[9,11] Although these patients are unlikely to exhibit audiologic improvement, we believe that anti-IL-5 therapy can prevent progression to profound sensorineural hearing loss, helping avoid cochlear implantation.[12]

Surgical treatment for EOM is not recommended.[13,14] Given the chronic and progressive nature of this disease, it often recurs after surgery. The viscous nature of the effusion contributes to surgical failure, through the obstruction of tympanostomy tubes as well as the impairment of middle ear mucus circulation. Only 1 patient in our study underwent otologic surgery after starting biologics. However, this procedure was performed to repair a tympanic membrane perforation that was present before the start of anti-IL-5 therapy.

Historically, systemic steroids have been used as first-line treatment for EOM.[15] Daily administration is required to prevent disease relapse yet is also associated with severe side effects and decreased patient compliance. Cessation of steroids will result in deterioration of hearing loss and effusion recurrence. Other medical treatments include antibiotics, heparin, and intratympanic steroids.[16] Although less morbid than systemic medications, intratympanic steroids may not be feasible given the highly viscous nature of the effusion, which acts as a barrier to medication delivery. Lifelong treatment is required to prevent disease recurrence and is inconvenient for patients. By comparison, monthly injections with IL-5 inhibitors can treat the disease and prevent recurrence with minimal side effects.

At the molecular level, IL-5 is the major cytokine responsible for the recruitment and activation of eosinophils.[14,17] In asthma and chronic rhinosinusitis, the level of IL-5 has been shown to correlate with disease severity.[17] Although in different anatomic locations, both disease processes involve local inflammation of a respiratory epithelium. In this retrospective review, anti-IL-5 therapy cleared effusions in 5 of 7 patients while effectively treating airway and sinus symptoms. These data suggest that the mucosa of the middle ear responds in a similar mechanism to that of the respiratory tract and paranasal sinuses. By extension, we recommend anti-IL-5 therapy as first-line treatment for EOM. Once a diagnosis of EOM is made, biologic therapy should be initiated as soon as possible to prevent further deterioration of hearing loss.

The review was limited by the retrospective nature of the study. The patients included did not have a documented diagnosis of EOM. However, 9 of 9 patients had documented diagnoses of eosinophilic asthma and chronic rhinosinusitis, and 8 of 9 patients had documented nasal polyposis. We believe that the presence of a chronic middle ear effusion represents a diagnosis of EOM in patients who exhibit these conditions, given their close clinical relationship. Also, since these patients were not routinely screened for otologic symptoms during treatment, the timeline of when their effusions cleared was inexact. This likely caused an overestimation of time to effusion clearance. There were limited audiometric data for this analysis. Future studies should include routine audiometric testing to evaluate the efficacy of IL-5 inhibitors in treating hearing loss.

Conclusion

EOM is an underrecognized disease. IL-5-directed therapies may prove effective in treating this recalcitrant form of chronic otitis media.

Author Contributions

Nathaniel K. Breslin, collected the patient data and contributed to the writing of the manuscript; **N. Hadley Heindel**, conceptualized and designed the project, collected the patient data and contributed to the writing of the manuscript; **Rex S. Haberman**, conceptualized and designed the project, collected the patient data and contributed to the writing of the manuscript.

Disclosures

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