Received: 16 September 2020 | Revised: 30 October 2020 | Accepted: 17 November 2020

DOI: 10.1002/lio2.508

REVIEW

Laryngoscope Investigative Otolaryngology

Autoimmune inner ear disease: A systematic review of management

Nathaniel K. Breslin BA[1] | Varun V. Varadarajan MD[2] | Eric S. Sobel MD[3] | Rex S. Haberman MD[4]

[1]University of Florida College of Medicine, Gainesville, Florida, USA

[2]Department of Otolaryngology—Head and Neck Surgery, The Ohio State University, Columbus, Ohio, USA

[3]Department of Medicine, Division of Rheumatology and Clinical Immunology, University of Florida, Gainesville, Florida, USA

[4]Department of Otolaryngology—Head and Neck Surgery, University of Florida, Gainesville, Florida, USA

Correspondence
Rex S. Haberman, Department of Otolaryngology, Department of Surgery, University of Florida, P.O. Box 100138, Gainesville, FL 32608-0138, USA.
Email: rex.haberman@ent.ufl.edu

Abstract

Objectives: The study systematically reviewed the existing literature on the management of autoimmune inner ear disease (AIED).

Study Design: Systematic review.

Methods: We performed a literature search of Embase, NCBI, Cochrane, and Web of Science databases from April 1990 to April 2020. Inclusion criteria included studies that were retrospective or prospective in nature evaluating the treatment of AIED with audiometric data measuring hearing outcomes during treatment. Hearing improvement was the primary study outcome and improvement in vestibular symptoms was the secondary study outcome.

Results: Sixteen of 412 candidate articles were included in our study. Systemic steroid treatment is most commonly described. Alternative treatment modalities included intratympanic steroid treatment, methotrexate, cyclophosphamide, azathioprine, infliximab, etanercept, adalimumab, golimumab, methylprednisolone, rituximab, and anakinra.

Conclusion: Systemic corticosteroids are the first line treatment of AIED. Intratympanic steroids are a potential adjuvant or alternative treatment for patients who cannot tolerate or become refractory to steroid treatment. Steroid nonresponders may benefit from biologic therapy. Alternative treatment modalities including nonsteroidal immunosuppressants and biologics have been studied in small cohorts of patients with varying results. Prospective studies investigating the efficacy of biologic and nonsteroidal therapy are warranted.

Level of Evidence: 2.

KEYWORDS

autoimmune inner ear disease

1 | INTRODUCTION

Autoimmune inner ear disease (AIED) is an uncommon inner ear disorder characterized by progressive and often fluctuating sensorineural hearing loss (SNHL).[1,2] McCabe first described AIED in 1979 with a case series of 18 patients with progressive, bilateral SNHL without an identifiable etiology. All patients responded to treatment with corticosteroids and cyclophosphamide.[1] AIED has remained a diagnostic

challenge, with minimal advances in our understanding of the pathogenesis. Current literature supports an autoimmune mediated mechanism given the identification of inner ear specific autoantibodies in the sera of patients with AIED, its co-existence with other autoimmune diseases, and its favorable response to immunosuppressant drugs.[1,2]

Diagnosis of AIED presents a unique challenge to clinicians due to the lack of standardized diagnostic criteria or reliable pathognomonic tests. AIED is a diagnosis of exclusion and is made through clinical evaluation, demonstration of SNHL with periodic audiologic testing, and response to immunomodulatory drugs.[1,2] Existing laboratory tests are controversial and there is no definite and widely accepted marker for the diagnosis of AIED, although several have been described.[3-7] The most frequently described marker in AIED is the antibody to Heat Shock Protein-70, although its utility has been debated.[8-11] The lack of widely accepted diagnostic criteria has prevented the foundation of large trials and created differences in the inclusion criteria for published studies. Most studies adhere to the diagnostic criteria defined by the following: (a) progressive, bilateral SNHL of at least 30 dB at one or more frequencies; (b) SNHL determined to be idiopathic based on clinical evaluation, blood tests, and MRI imaging.[12] Given the autoimmune origin, many studies include only cases with bilateral hearing loss. However, there are reports AIED can take years to develop bilaterally, leading other trials to include cases with unilateral hearing loss.[13] Also, some studies include patients with Meniere's disease, given the clinical overlap between these two conditions, while other studies exclude these patients.[14]

Steroids are the mainstay treatment for AIED, however, responsiveness is variable and may diminish over time. Fewer than 14% of patients remain steroid responsive by 34 months.[15,16] Currently, there are no consensus treatment recommendations for management of AIED. The objective of this systematic review is to (a) evaluate the hearing and vestibular outcomes of AIED treatment modalities; (b) compare the outcomes of steroid and biologic therapies; (c) create a treatment algorithm based on steroid responsiveness. There are currently two systematic reviews published on the treatment of AIED.[17,18] These reviews support steroids as first-line treatment for AIED given the lack of a clear alternative medication with sufficient supporting data. Although these reviews effectively review the literature, they do not provide evidence-based algorithms directing the work-up and treatment of AIED.

2 | METHODS

2.1 | Search and selection

A review was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Embase, Pubmed, Cochrane, and Web of Science databases were reviewed. A manual search was also conducted and supplemented the database. The search key terms included the following: "autoimmune inner ear disease" followed by a list of modifiers including steroids, prednisone, methotrexate, cyclophosphamide, infliximab, etanercept, golimumab, intratympanic methylprednisolone, intratympanic dexamethasone, rituximab, anakinra, azathioprine, biologics, and cochlear implant. For example, the first search term was "autoimmune inner ear disease AND steroids." The second term was "autoimmune inner ear disease AND prednisone." This was continued to include all listed treatment options for this disease. In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, two independent researchers (NKB and VVV) screened the literature to review eligibility based on the title and abstract, following inclusion and exclusion criteria. References of articles were screened for inclusion.

2.2 | Inclusion and exclusion criteria

Inclusion criteria for this review were: (a) studies involving the treatment of AIED with audiometric data on hearing outcomes, (b) studies that are prospective or retrospective in nature, (c) studies published from April 1990 to April 2020. Dates were decided due to trends in research on AIED. Exclusion criteria were: (a) case reports, (b) studies with less than 4 subjects, (c) studies that monitored hearing subjectively without audiometric data.

2.3 | Data extraction and analysis

The data extracted included sample size, study design, treatment modality, audiometric data, and reported vestibular symptoms. Primary outcome was hearing improvement and secondary outcome was vestibular symptom improvement. Hearing improvement was defined as threshold shift ≥15 dB at one frequency, ≥10 dB at two or more consecutive frequencies, or a 12% change in discrimination score within 3 months of starting therapy, when defined. Vestibular symptoms were measured subjectively, as the exact criteria for improvement in vestibular symptoms was not clearly defined by each individual author. Primary and secondary outcomes from these studies are outlined in Table 1 and discussed below. There was significant heterogeneity among studies in how the primary and secondary study outcomes were assessed. The results from each study were not pooled and a qualitative comparison was performed.

2.4 | Level of evidence

The level of evidence for each specific study was categorized using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Table 2). Level 1 was defined as systematic review of randomized trials; Level 2 was defined as randomized or observational study with dramatic effect; Level 3 was defined as nonrandomized controlled cohort/follow-up study; Level 4 was defined as case series, case control, or historically controlled study.

TABLE 1 Systematic review of treatment for autoimmune inner ear disease

Author	Title of study	Type of study	Sample size	Treatment regimen	Hearing loss improved	Vestibular Sx. improved
Niparko et al 2005	Serial audiometry in a clinical trial of AIED treatment	Prospective case series	116	Oral prednisone (60 mg/day for 4 weeks)	69/116 (59.5%)	Not reported
Zeitoun et al 2005	Corticosteroid response and supporting cell antibody in autoimmune hearing loss	Prospective case series	63	Oral prednisone (60 mg/day) or methylprednisolone (24 mg tapered by 4 mg daily for 6 days)	28/63 (44%)	Not reported
Matteson et al 2001	Open trial of methotrexate as treatment for autoimmune hearing loss	Prospective open label	17	Oral methotrexate (initial dose of 7.5 mg increasing to 25 mg per week)	11/17 (65%)	Not reported
Harris et al 2003	Treatment of corticosteroid-responsive autoimmune inner ear disease with methotrexate: a randomized controlled trial	Prospective RCT	33	Methotrexate (15-20 mg per week w/prednisone) vs prednisone alone	24/30(80%) methotrexate vs 29/31(94%) control group	Not reported
Salley et al 2001	Methotrexate in management of immune mediated cochleovestibular disorder	Prospective open label	50	Oral methotrexate (initial dose of 7.5 mg increasing to 25 mg per week)	25/47 (53%)	27/39 (69%)
Sismanis et al 1994	Methotrexate therapy for autoimmune hearing loss: a preliminary report	Prospective open label	25	Oral methotrexate (initial dose of 7.5 mg increasing to 25 mg per week)	80%	100%
Garcia-Berrocal et al 2006	Alternatives to systemic steroids for refractory immune mediated ear disease: a physiopathologic approach	Retrospective case series	5	Oral methotrexate (initial dose of 7.5 mg increasing to 25 mg per week)	0%	100%
			11	Intratympanic methylprednisolone (0.3-0.5 mL 40 mg/mL once per week for 2 months)	69%	100%
Broughton et al 2004	Immune mediated ear disease: 10 year experience	Retrospective chart review	6	Cyclophosphamide (dosage and duration not clear)	2/6 (33%)	Not reported
Lasak et al 2001	Autoimmune ear disease: steroid and cytotoxic drug therapy	Retrospective chart review	10	Cyclophosphamide (100 mg twice a day)	5/10 (50%)	Not reported
			7	Azathioprine (100 mg twice a day)	5/7 (71%)	Not reported
			23	Methotrexate (7.5 mg to 15 mg per week for 6 months)	14/23 (61%)	Not reported
Rahman et al 2001	Etanercept therapy for immune-mediated cochleovestibular disorders: preliminary results in a pilot study	Retrospective case series	12	Etanercept (25 mg SC injections twice a week for 6-12 months)	11/12 (92%)	7/8 (88%)
Matteson et al 2005	Etanercept therapy for immune-mediated cochleovestibular disorders: a multi-center, open-label, pilot study	Prospective open label	23	Etanercept (25 mg SC injections twice a week for 24 weeks)	7/23 (30%)	8/16 (50%)
Derebery et al 2014	An open label study to evaluate the safety and efficacy of intratympanic golimumab therapy in patients with autoimmune inner ear disease	Prospective open label	7 per protocol	Intratympanic golimumab (0.3 mL injection on days 0, 7, 21, and 35)	2/7 (28.5%)	Not reported

(Continues)

TABLE 1 (Continued)

Author	Title of study	Type of study	Sample size	Treatment regimen	Hearing loss improved	Vestibular Sx. improved
Van Wijk et al 2006	Local perfusion of the tumor necrosis factor alpha blocker infliximab to the inner ear improves autoimmune neurosensory hearing loss	Prospective open label	4	Transtympanic infliximab (0.3 mL once weekly for 4 weeks)	3/4 (75%)	Not reported
Cohen et al 2011	A pilot study of rituximab in immune-mediated inner ear disease	Prospective open label	7	Rituximab (1000 mg on day 14 and 15 from baseline visit)	5/7 (71.4%)	Not reported
Matsuoka et al 2013	Autoimmune inner ear disease: a retrospective review of 47 patients	Retrospective chart review	5	Rituximab (1000-1200 mg initial infusion followed by 1000 mg on day 15)	2/5 (40%)	5/5 (100%)
			10	Adalimumab (40 mg/week for 2 weeks)	1/10 (10%)	8/10 (80%)
			30	Intratympanic prednisone (dosage and duration not clear)	15/30 (50%)	Not reported
			47	Oral prednisone (1 mg/kg/day for 2-4 weeks)	33/47 (70.2%)	Not reported
Vambutas et al 2014	Early efficacy trial of anakinra in corticosteroid-resistant autoimmune inner ear disease	Prospective open label	10 per protocol	Anakinra (100 mg SC injection for 84 days)	7/10 (70%)	Not reported

2.5 | Bias assessment

Risk of bias was assessed using a Downs and Black Checklist. This system contains 28 "yes or no" questions across 5 sections: study quality (10), external validity (3), study bias (7), confounding and selection bias (6), and power of the study (1). Down and Black score ranges were then given corresponding quality levels: excellent (26–28), good (20–25), fair (15–19), and poor (<15). The quality of each study included in this review was assessed using this checklist and is reported in Table 2.

3 | RESULTS

3.1 | Study selection

Four hundred and twelve abstracts were reviewed from four databases. Three hundred fifty-nine articles remained after removal of duplicates. These studies were reviewed for relevance to the project with emphasis on finding prospective or retrospective trials involving treatment of AIED with audiometric data to monitor patient responsiveness. After review, 18 articles met criteria. Two of the remaining articles were excluded because they were case reports, leaving a total of 16 articles to review (Figure 1).

3.2 | Study characteristics

Of the remaining 16 articles, there were eight prospective open label trials, two prospective case series, one prospective randomized controlled trial, three retrospective chart reviews, and two retrospective case series. Sample sizes were relatively small with a mean 29.8 [SD 28.2]. Patient characteristics were similar among studies and are described in Table 2. Table 1 includes a description of interventions, comparisons, outcomes, timing, and design of each study.

4 | DISCUSSION

4.1 | Diagnosis

Initial evaluation of AIED should focus on the quality and timing of symptoms as well as the presence of associated otologic or systemic symptoms. Patients should be screened for predisposing factors to SNHL as up to 30% of patients with AIED have a coexisting systemic autoimmune disease.[19,20] A thorough review of systems should be taken in cooperation with rheumatology to rule out a systemic autoimmune process.[20,21] MRI is typically obtained to rule out retrocochlear pathology.[3] Although there is no correlation between cochlear enhancement on MRI and proven AIED, MRI with intratympanic gadolinium may have utility in diagnosing AIED through detection of inner ear gadolinium.[22,23] If MRI is negative, work-up should be continued with laboratory evaluation to confirm the diagnosis. The authors obtain a complete blood count with differential,

TABLE 2 Patient characteristics, level of evidence, and bias

Author	Title of study	Patient characteristics	Level of evidence	Quality assessment
Niparko et al 2005	Serial audiometry in a clinical trial of AIED treatment	53 females, 63 males Mean age 48.8 years	4	Good (20)
Zeitoun et al 2005	Corticosteroid response and supporting cell antibody in autoimmune hearing loss	30 females, 33 males Mean age 47 years	4	Fair (18)
Matteson et al 2001	Open trial of methotrexate as treatment for autoimmune hearing loss	10 females, 7 males Mean age 48.8 years	2	Fair (19)
Harris et al 2003	Treatment of corticosteroid-responsive autoimmune inner Ear disease with methotrexate: a randomized controlled trial	29 females, 38 males Mean age not given	2	Excellent (26)
Salley et al 2001	Methotrexate in management of immune mediated cochleovestibular disorder	28 females, 25 males Mean age 50.5 years	2	Good (21)
Sismanis et al 1994	Methotrexate therapy for autoimmune hearing loss: a preliminary report	3 females, 2 males Mean age 48.8 years	2	Fair (18)
Garcia-Berrocal et al 2006	Alternatives to systemic steroids for refractory immune mediated ear disease: a physiopathologic approach	9 females, 7 males Mean age 39 years	4	Fair (19)
Broughton et al 2004	Immune mediated ear disease: 10 year experience	Not defined	3	Poor (10)
Lasak et al 2001	Autoimmune ear disease: steroid and cytotoxic drug therapy	30 females, 32 males Mean age 50 years	2	Good (21)
Rahman et al 2001	Etanercept therapy for immune-mediated cochleovestibular disorders: preliminary results in a pilot study	6 females, 6 males Mean age 47 years	4	Fair (14)
Matteson et al 2005	Etanercept therapy for immune-mediated cochleovestibular disorders: a multi-center, open-label, pilot study	12 females, 11 males Mean age 48 years	2	Fair (19)
Derebery et al 2014	An open label study to evaluate the safety and efficacy of intratympanic golimumab therapy in patients with autoimmune inner ear disease	3 females, 7 males Mean age 58.6 years	2	Good (21)
Van Wijk et al 2006	Local perfusion of the tumor necrosis factor alpha blocker infliximab to the inner ear improves autoimmune neurosensory hearing loss.	4 females, 0 males Mean age 46 years	2	Good (20)
Cohen et al 2011	A pilot study of rituximab in immune-mediated inner ear disease	Gender not given Mean age 47 years	2	Fair (18)
Matsuoka et al 2013	Autoimmune inner ear disease: a retrospective review of 47 patients	Not defined	4	Poor (14)
Vambutas et al 2014	Early efficacy trial of anakinra in corticosteroid-resistant autoimmune inner ear disease	5 females, 6 males Mean age 47.3 years	2	Good (20)

Abbreviations: RCT, randomized controlled trial; SC, subcutaneous; Sx, symptoms.

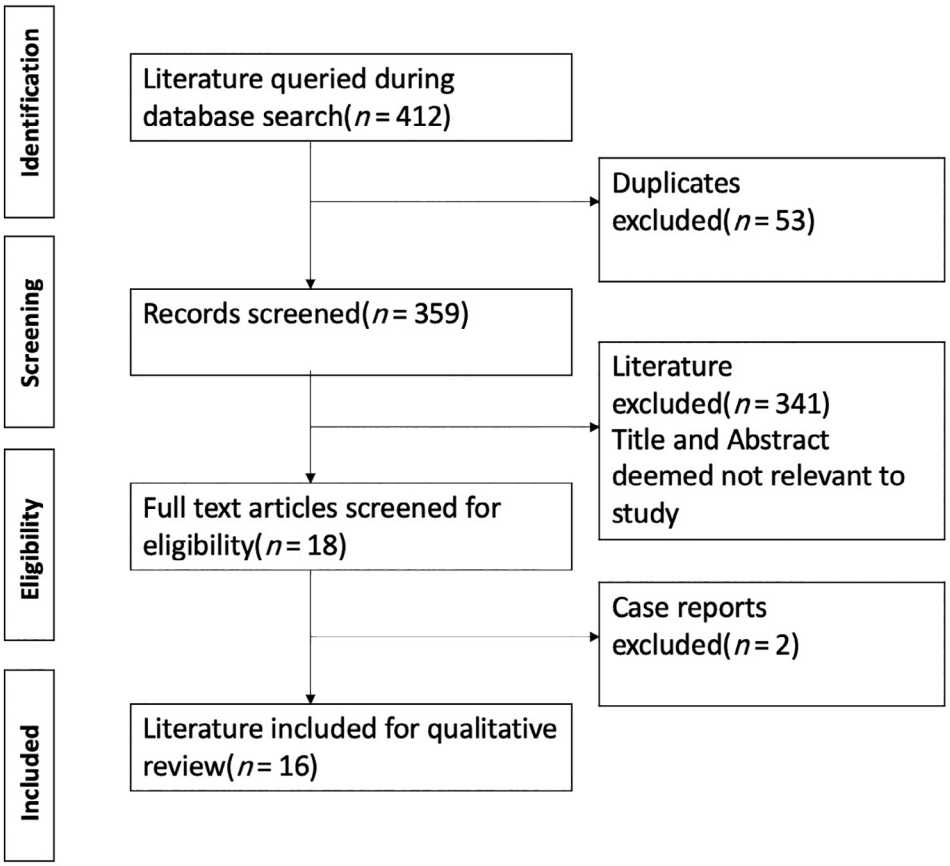

FIGURE 1 Search strategy flow diagram

anti-HSP 70 antibody, and erythrocyte sedimentation rate (ESR) in every patient with suspected AIED. Garcia-Berrocal et al reported a decreased concentration of CD4+ and CD8+ cells in patients with AIED compared to healthy controls, aiding in differentiation of primary AIED against a systemic autoimmune process.[24] Figure 2 proposes a stepwise approach for the diagnosis of AIED. Recognizing steroid responsiveness aids in diagnosis and is critical for directing treatment.

4.2 | Oral steroids

Since McCabe's initial case series, oral steroids have remained the first-line treatment for AIED.[1] Zeltoun et al and Matsuoka et al reported audiologic improvement in 28 (44%) and 11 (71.4%) patients treated with oral steroids, respectively.[13,25] In a 2005 study, 116 patients were treated with a 1-month course of oral prednisone (60 mg/day), during which time they underwent serial audiometry. Sixty-nine (59.5%) of these patients showed improvements in word indication score (WIS) ranging from 2-80% and 62 (53.5%) patients showed 1 dB or more improvement in pure tone averages.[26]

4.3 | Intratympanic steroids

Intratympanic (IT) steroid injections have been used to treat AIED in patients who do not respond to oral steroids or cannot tolerate long-term treatment. Side effects associated with IT steroids are much fewer than oral steroids and include transient dizziness, injection site pain, vertigo, tongue numbness, and a small perforation of the tympanic membrane.[27] Matsuoka et al reported a 50% response rate among patients treated with IT steroids.[13] However, it is unclear whether these patients previously received other treatments. Garcia-Berrocal used IT methylprednisolone to treat 11 patients who responded poorly to oral steroids, three of which also did not improve with methotrexate. Six patients (68.75%) showed an improvement in hearing with weekly IT steroids and all patients affected by vestibular symptoms improved.[28] Of note, there are also case reports describing audiologic improvement with IT steroids that did not meet the inclusion criteria for this study.[29-31]

4.4 | Nonsteroidal immunosuppressants

Cyclophosphamide exerts its effects through the alkylation of DNA, inhibiting protein synthesis.[32] McCabe used cyclophosphamide in conjunction with steroids for treatment of AIED with promising results, demonstrating an average 15 dB pure tone improvement and 20% speech discrimination score improvement.[1] Since this time, studies have been limited and data has shown poor results in hearing improvement with cyclophosphamide.[16,33] Cyclophosphamide is no longer frequently used to treat AIED due to its side effect profile which includes gonadal, bladder, and bone marrow toxicity.[32]

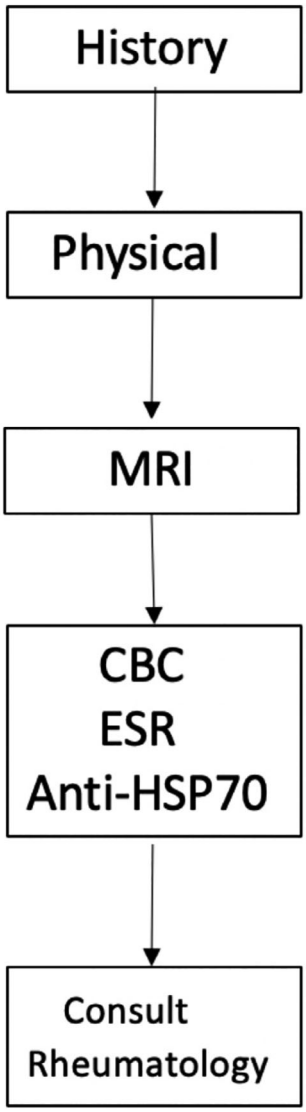

FIGURE 2 Proposed diagnostic algorithm for autoimmune inner ear disease

Methotrexate is used as an alternative treatment for refractory AIED; it works by inhibiting the enzyme dihydrofolate reductase, preventing the synthesis of nucleotides necessary for DNA and RNA formation.[34] Methotrexate has better long-term tolerability than cyclophosphamide; the most common side effects are nausea, vomiting, and mucosal ulcers. The major adverse effect of methotrexate is hepatotoxicity, which can be prevented with folic acid supplementation.[34] Treatment outcomes have varied with hearing improvement ranging from 0% to 70%.[12,28,35-37] Methotrexate appears to be more efficacious in treating vestibular symptoms with reported subjective improvements in 80% to 100% of patients.[12,28,35-37]

4.5 | Biologics

Multiple biologic agents have been used to treat AIED. TNF-α is a proinflammatory cytokine that has been targeted by several drugs including the following: etanercept, infliximab, golimumab, and adalimumab. These drugs are generally well tolerated. However, there is potential for severe side effects including reactivation of tuberculosis and development of malignancies.[38] High levels of circulating TNF-α are predictive of steroid-sensitive disease, making TNF-α an attractive target in steroid refractory AIED.[39] A pilot study investigating treatment with systemic etanercept showed promising results with 58% of patients experiencing improved hearing.[40] A study conducted 4 years later showed hearing improvement in only 30% of patients treated with etanercept.[41] Since then, there have been two trials investigating the efficacy of intratympanic TNF-α inhibitors. In a 2006 study conducted by Van Wijk et al, trans-tympanic infliximab allowed full steroid tapering without loss of hearing function in 4/5 steroid-dependent patients. Three out of four patients treated with only trans-tympanic infliximab demonstrated clinically significant hearing recovery.[42] In a 2014 study conducted by Derebery et al, 10 patients with steroid dependent AIED were treated with intratympanic golimumab therapy.[43] Of the 7 patients able to tolerate treatment protocol, five showed stable pure tone averages, four showed stable word recognition score, two experienced an improvement in word recognition scores and golimumab treatment allowed complete tapering of prednisone in all 7 patients.[43]

Rituximab is a monoclonal antibody directed against the CD20 B-cell antigen, exerting cytotoxic effects against B-cells and preventing antibody formation. Rituximab has been used to treat steroid refractory AIED and common side effects include transfusion reaction, cytopenias, headache, and hair loss.[44] A pilot student showed post-steroid hearing improvement in 5/7 patients treated with rituximab.[45] A recent retrospective study showed hearing improvement in 2/5 patients and vestibular improvement in 5/5 patients treated with rituximab.[13]

Anakinra is an IL-1 receptor antagonist that prevents formation of the proinflammatory cytokine IL-1β.[46] Anakinra has shown promising results in the treatment of steroid-resistant AIED.[46] A phase I/II single arm clinical trial showed audiometric improvement in 70% of steroid resistant patients who completed per-protocol treatment with anakinra.[46] Three of these subjects relapsed upon discontinuation of treatment and their relapse was correlated with increased plasma IL-1β levels.[46] The drug was well tolerated and side effects were limited to injection site reactions.[46,47] Other potential side effects include nausea, diarrhea, headache, sore throat, and congestion.[48]

4.6 | Treatment protocol

To date, there are no prospective or randomized clinical trials investigating initial treatment protocols. The management protocol proposed by Rauch et al is accepted by many authors.[49] Treatment should begin with a 1-month steroid challenge at 1 mg/kg/day with an upper limit of 60 mg/day. Pure tone audiometry and speech discrimination testing is performed before treatment is initiated and after completion. If hearing is improved after 4 weeks, determined by threshold shift ≥15 dB at one frequency, ≥10 dB at two or more consecutive

frequencies, or a 12% increase in word recognition score, the patient is deemed a steroid responder. Steroid responders are continued on full dose therapy with monthly audiometry until they reach a plateau of recovery; then they are tapered over 8 weeks to a maintenance daily dose of 10 to 20 mg for approximately 6 months.[49] Steroid responsiveness often diminishes over time and less than 14% of patients remain steroid responsive by 34 months.[15,16] Patients who do not respond to the 4-week steroid challenge are deemed nonresponders and are tapered off steroids over 12 days.[49]

Despite their efficacy as first line treatment for AIED, long-term systemic steroid therapy is associated with significant morbidity, adverse effects, and decreased patient compliance. A reasonable alternative for patients unable to tolerate oral steroids or noncompliant with treatment is biweekly (once every 2 weeks) 4 mg/mL intratympanic dexamethasone injections for 6 months, started after patients reach a plateau of recovery demonstrated by monthly audiograms. Earlier administration of intratympanic steroids should also be considered in patients with significant medical comorbidities. Intratympanic treatment has been shown to improve hearing in patients refractory to steroids and it has two main benefits: it involves localized direct drug delivery to the affected site, and it produces significantly higher levels of steroids in the perilymph compared to systemic administration.[28,30,50] If hearing loss progresses despite systemic and intratympanic steroids, biologic or other immunosuppressant therapy should be initiated in collaboration with rheumatology.

Literature review yielded no clear recommendation for patients refractory to steroids. Treatment of steroid resistant autoimmune ear disease is challenging and there are currently no universal guidelines. Results varied widely in regards to hearing improvement among the multiple different medications assessed in this systematic review. Studies assessing hearing outcomes in steroid nonresponders are limited and many of these patients eventually experience significant hearing decline.[46,47] One study revealed that steroid-resistant patients have higher circulating plasma levels of IL-1β as compared with steroid-responsive patients.[51] IL-1β is aberrantly regulated in steroid nonresponders and dexamethasone showed greater ability to repress IL-1β transcription in clinical steroid responders than in nonresponders.[51,52] In our systematic review, the IL-1β antagonist anakinra showed promising results with 70% of steroid-resistant patients experiencing hearing improvement with daily anakinra injections.[46]

Given the promising early data, supporting biochemical evidence, and lack of alternative treatment options, these authors believe anakinra should be considered as a potential treatment option for patients that fail the 1-month steroid challenge. Current treatment protocols for Anakinra involve daily 100 mg subcutaneous injections. If patients show audiometric improvement with anakinra, monthly or bimonthly canakinumab (IL-1β antagonist) injections may be considered as an alternative treatment. Canakinumab requires less frequent injections than anakinra.[53] Post-steroid treatment decisions should be

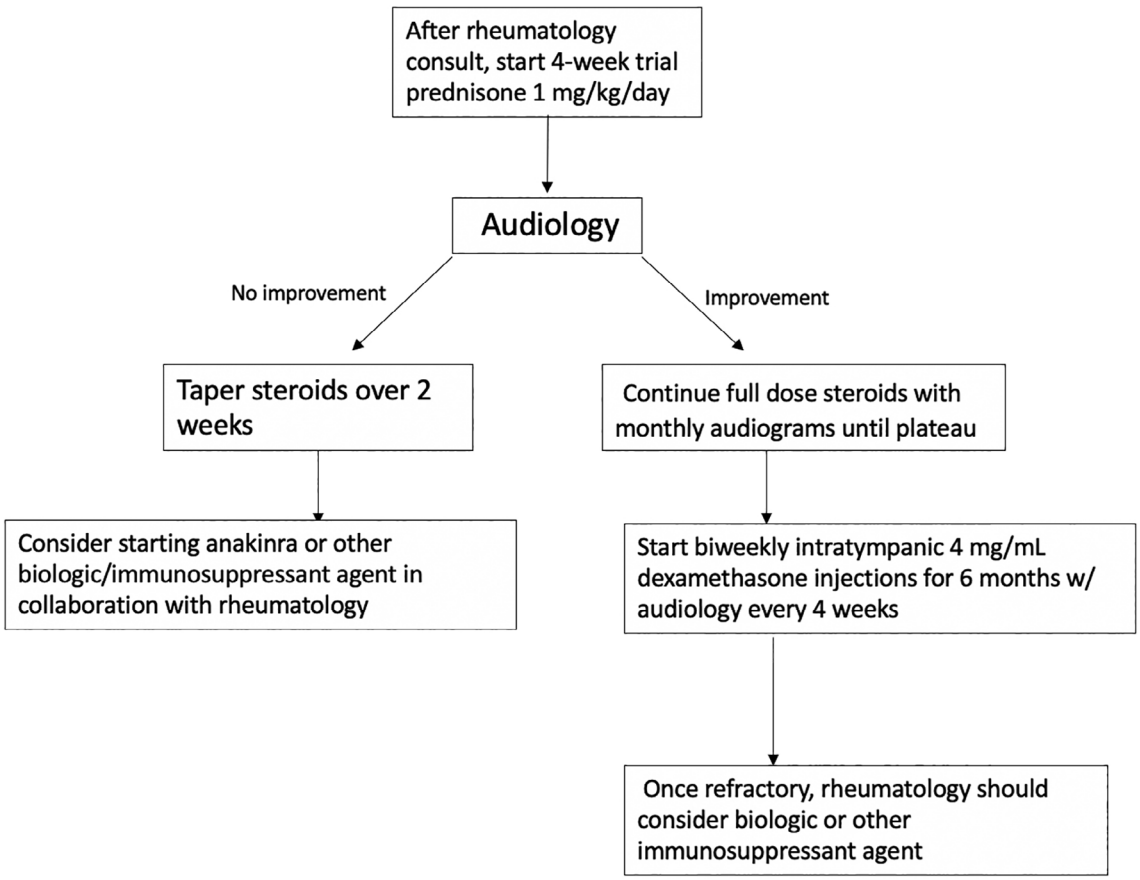

FIGURE 3 Proposed treatment algorithm for autoimmune inner ear disease

made in collaboration by otolaryngology and rheumatology and in consideration of the patient's specific clinical presentation and medical comorbidities. Figure 3 proposes a novel treatment algorithm for both steroid-responsive and steroid-resistant patients.

4.7 | Future directions

Prospective clinical trials are warranted to guide treatment in steroid-refractory patients as well as to compare the effectiveness of systemic vs intratympanic steroids and biologic therapy. After a 1-month steroid challenge, patients who demonstrate steroid responsiveness could be randomized to receive 6 months of treatment with either systemic or intratympanic steroid treatment. If intratympanic steroids demonstrate similar results to systemic administration in terms of hearing stabilization, they should be considered as the preferred treatment for steroid-responsive AIED patients. Steroid-refractory patients could also be randomized to receive either subcutaneous or intratympanic IL-1β antagonist therapy (eg, anakinra or canakinumab) to investigate the efficacy of these relatively novel treatment modalities. One potential advantage of intratympanic canakinumab is its longer half-life, meaning less frequent intratympanic injections, sustained action in the inner ear, and potential lower dosages required.

Patients who fail traditional steroid treatment or are unable to tolerate long-term immunosuppressant therapy generally progress to profound SNHL requiring cochlear implantation (CI).[54] We recommend CI evaluation when patients demonstrate sustained audiometric progression towards nonserviceable hearing. Early evaluation for cochlear implantation allows patients to become familiar with the technology and establish baseline audiometric performance. Many of these patients will ultimately progress to CI candidacy given the potentially rapid deterioration in hearing associated with AIED.

During treatment for AIED, frequent audiometry can help identify useful agents and modify treatment planning based on audiologic response. Mobile tablet audiometry using an iPad audiometer has emerged as a reliable way to monitor a patient's clinical progression over time, creating a more dynamic and personalized treatment course for each patient.[55]

This review was limited by the heterogeneity of the studies' inclusion criteria for the diagnosis of AIED. However, given the paucity of literature concerning the treatment of AIED and its clinical presentation, these authors adhered to each author's diagnostic criteria when reviewing their study. The review is also limited by paucity in the literature formally investigating potential treatment options in steroid-resistant patients. Also, the lack of long-term follow-up limited our understanding of the natural history of the disease and whether promising treatment modalities, such as intratympanic steroids, therapeutic effect may wear off over time.

5 | CONCLUSION

Systematic review revealed that steroids remain the mainstay treatment for AIED. Intratympanic steroid injections has emerged a potential alternative treatment with greater long-term tolerability. Biologic therapy, such as anakinra, should be started in collaboration with rheumatology in patients who fail the initial 4-week steroid challenge. There is a need in the literature for randomized controlled trials further investigating biologic therapy and intratympanic medication delivery.

CONFLICT OF INTEREST

The authors whose names are listed above certify that they have no affiliations with or any involvement in any organization or entity with any financial or nonfinancial interest in the subject matter or materials discussed in this article.

ORCID

Rex S. Haberman https://orcid.org/0000-0001-5197-7979

BIBLIOGRAPHY

1. Mccabe BF. Autoimmune sensorineural hearing loss. *Ann Otol Rhinol Laryngol*. 2004;113(7):526-520.
2. Vambutas A, Pathak S. AAO: autoimmune and autoinflammatory (disease) in otology: what is new in immune-mediated hearing loss. *Laryngosc Investig Otolaryngol*. 2016;1(5):110-115.
3. Mijovic T, Zeitouni A, Colmegna I. Autoimmune sensorineural hearing loss: the otology-rheumatology interface. *Rheumatol (UK)*. 2013;52(5):780-789.
4. Yoo TJ, Tanaka H, Kwon SS, et al. β-Tubulin as an autoantigen for autoimmune inner ear disease. *Int Congr Ser*. 2003;1240(C):1207-1210.
5. Cadoni G, Agostino S, Manna R, et al. Clinical associations of serum antiendothelial cell antibodies in patients with sudden sensorineural hearing loss. *Laryngoscope*. 2003;113(5):797-801.
6. Boulassel MR, Tomasi JP, Deggouj N, Gersdorff M. Identification of β-actin as a candidate autoantigen in autoimmune inner ear disease. *Clin Otolaryngol Allied Sci*. 2000;25(6):535-541.
7. Kommareddi PK, Nair TS, Vallurupalli M, et al. Autoantibodies to recombinant human CTL2 in autoimmune hearing loss. *Laryngoscope*. 2009;119(5):924-932.
8. Yeom K, Gray J, Nair TS, et al. Antibodies to HSP-70 in normal donors and autoimmune hearing loss patients. *Laryngoscope*. 2003;113(10):1770-1776.
9. Ianuale C, Cadoni G, De Feo E, et al. A systematic review and meta-analysis of the diagnostic accuracy of anti-heat shock protein 70 antibodies for the detection of autoimmune hearing loss. *Otol Neurotol*. 2013;34(2):214-219.
10. Bonaguri C, Orsoni JG, Zavota L, et al. Anti-68 kDa antibodies in autoimmune sensorineural hearing loss: are these autoantibodies really a diagnostic tool? *Autoimmunity*. 2007;40(1):73-78.
11. García Berrocal JR, Ramírez-Camacho R, Arellano B, Vargas JA. Validity of the Western blot immunoassay for heat shock protein-70 in associated and isolated immunorelated inner ear disease. *Laryngoscope*. 2002;112(2):304-309.
12. Harris JP, Weisman MH, Derebery JM, et al. Treatment of corticosteroid-responsive autoimmune inner ear disease with methotrexate: a randomized controlled trial. *JAMA*. 2003;290(14):1875-1883.
13. Matsuoka AJ, Harris JP. Autoimmune inner ear disease: a retrospective review of forty-seven patients. *Audiol Neurotol*. 2013;18(4):214-221.
14. Cohen S, Shoup A, Weisman MH, Harris J. Etanercept treatment for autoimmune inner ear disease: results of a pilot placebo-controlled study. *Otol Neurotol*. 2005;26(5):903-907.

15. Alexander TH, Weisman MH, Derebery JM, et al. Safety of high-dose corticosteroids for the treatment of autoimmune inner ear disease. *Otol Neurotol*. 2009;30(4):443-448.
16. Broughton SS, Meyerhoff WE, Cohen SB. Immune-mediated inner ear disease: 10-year experience. *Semin Arthritis Rheum*. 2004;34(2):544-548.
17. Strum D, Kim S, Shim T, Monfared A. An update on autoimmune inner ear disease: a systematic review of pharmacotherapy. *Am J Otolaryngol—Head Neck Med Surg*. 2020;41(1):102310.
18. Brant JA, Eliades SJ, Ruckenstein MJ. Systematic review of treatments for autoimmune inner ear disease. *Otol Neurotol*. 2015;36(10):1585-1592.
19. Loveman DM, De Comarmond C, Cepero R, Baldwin DM. Autoimmune sensorineural hearing loss: clinical course and treatment outcome. *Semin Arthritis Rheum*. 2004;34(2):538-543.
20. Bovo R, Aimoni C, Martini A. Immune-mediated inner ear disease. *Acta Otolaryngol*. 2006;126(10):1012-1021.
21. Ciorba A, Corazzi V, Bianchini C, et al. Autoimmune inner ear disease (AIED): a diagnostic challenge. *Int J Immunopathol Pharmacol*. 2018;32:2058738418808680.
22. Lobo D, Tuñón M, Villarreal I, Brea B, García-Berrocal JR. Intratympanic gadolinium magnetic resonance imaging supports the role of endolymphatic hydrops in the pathogenesis of immune-mediated inner-ear disease. *J Laryngol Otol*. 2018;132(6):554-559.
23. Zavod MB, Sataloff RT, Rao VM. Frequency of cochlear enhancement on magnetic resonance imaging in patients with autoimmune sensorineural hearing loss. *Arch Otolaryngol—Head Neck Surg*. 2000;126(8):969-971.
24. Garda-Berrocal JR, Vargas JA, Ramírez-Camacho RA, et al. Deficiency of naive T cells in patients with sudden deafness. *Arch Otolaryngol—Head Neck Surg*. 1997;123(7):712-717.
25. Zeitoun H, Beckman JG, Arts HA, et al. Corticosteroid response and supporting cell antibody in autoimmune hearing loss. *Arch Otolaryngol—Head Neck Surg*. 2005;131(8):665-672.
26. Niparko JK, Wang NY, Rauch SD, et al. Serial audiometry in a clinical trial of AIED treatment. *Otol Neurotol*. 2005;26(5):908-917.
27. Liu Y-C, Chi F-H, Yang T-H, Liu T-C. Assessment of complications due to intratympanic injections. *World J Otorhinolaryngol Neck Surg*. 2016;2(1):13-16.
28. García-Berrocal JR, Ibáñez A, Rodríguez A, et al. Alternatives to systemic steroid therapy for refractory immune-mediated inner ear disease: a physiopathologic approach. *Eur Arch Oto-Rhino-Laryngol*. 2006;263(11):977-982.
29. Yukawa K, Hagiwara A, Ogawa Y, et al. Bilateral progressive hearing loss and vestibular dysfunction with inner ear antibodies. *Auris Nasus Larynx*. 2010;37(2):223-228.
30. Harris DA, Mikulec AA, Carls SL. Autoimmune inner ear disease preliminary case report: audiometric findings following steroid treatments. *Am J Audiol*. 2013;22(1):120-124.
31. Zibelman M, Pollak N, Olszanski AJ. Autoimmune inner ear disease in a melanoma patient treated with pembrolizumab. *J Immunother Cancer*. 2016;4(1):4-8.
32. Stork CM, Schreffler SM. Cyclophosphamide. *Encyclopedia of Toxicology: Third Edition*. New York: Elsevier; 2014.
33. Lasak JM, Sataloff RT, Hawkshaw M, Carey TE, Lyons KM, Spiegel JR. Autoimmune inner ear disease: steroid and cytotoxic drug therapy. *Ear Nose Throat J*. 2001;80(11):808-815.
34. Mager DR. Methotrexate. *Home Healthc Now*. 2015;33(3):139-141.
35. Matteson EL, Fabry DA, Facer GW, et al. Open trial of methotrexate as treatment for autoimmune hearing loss. *Arthritis Rheum*. 2001;45(2):146-150.
36. Salley J, Grimm M, Sismanis A, Spencer RF, Wise CM. Methotrexate in the management of immune mediated cochleovestibular disorders: clinical experience with 53 patients. *J Rheumatol*. 2001;28(5):1037-1040.
37. Sismanis A, Thompson T, Willis HE. Methotrexate therapy for autoimmune hearing loss: a preliminary report. *Laryngoscope*. 1994;104(8):932-934.
38. Nash PT, Florin THJ. Tumour necrosis factor inhibitors. *Med J Aust*. 2005;183(4):205-208.
39. Svrakic M, Pathak S, Goldofsky E, et al. Diagnostic and prognostic utility of measuring tumor necrosis factor in the peripheral circulation of patients with immune-mediated sensorineural hearing loss. *Arch Otolaryngol – Head Neck Surg*. 2012;138(11):1052-1058.
40. Rahman MU, Poe DS, Choi HK. Etanercept therapy for immune-mediated cochleovestibular disorders: preliminary results in a pilot study. *Otol Neurotol*. 2001;22(5):619-624.
41. Matteson EL, Choi HK, Poe DS, et al. Etanercept therapy for immune-mediated cochleovestibular disorders: a multi-center, open-label, pilot study. *Arthritis Care Res*. 2005;52(3):337-342.
42. Van Wijk F, Staecker H, Keithley E, Lefebvre PP. Local perfusion of the tumor necrosis factor α blocker infliximab to the inner ear improves autoimmune neurosensory hearing loss. *Audiol Neurotol*. 2006;11(6):357-365.
43. Derebery MJ, Fisher LM, Voelker CCJ, Calzada A. An open label study to evaluate the safety and efficacy of intratympanic golimumab therapy in patients with autoimmune inner ear disease. *Otol Neurotol*. 2014;35(9):1515-1521.
44. Kasi PM, Tawbi HA, Oddis CV, Kulkarni HS. Clinical review: serious adverse events associated with the use of rituximab – a critical care perspective. *Crit Care*. 2012;164(4):231.
45. Cohen S, Roland P, Shoup A, et al. A pilot study of rituximab in immune-mediated inner ear disease. *Audiol Neurotol*. 2011;16(4):214-221.
46. Vambutas A, Lesser M, Mullooly V, et al. Early efficacy trial of anakinra in corticosteroid-resistant autoimmune inner ear disease. *J Clin Invest*. 2014;124(9):4115-4222.
47. Sakano H, Harris JP. Emerging options in immune-mediated hearing loss. *Laryngosc Investig Otolaryngol*. 2019;4(1):102-108.
48. Kullenberg T, Löfqvist M, Leinonen M, Goldbach-Mansky R, Olivecrona H. Long-term safety profile of anakinra in patients with severe cryopyrin-associated periodic syndromes. *Rheumatol (UK)*. 2016;55(8):1499-1506.
49. Rauch SD. Clinical management of immune-mediated inner-ear disease. *Ann N Y Acad Sci*. 1997;830:203-210.
50. Parnes LS, Sun A-H, Freeman DJ. Corticosteroid pharmacokinetics in the inner ear fluids: an animal study followed by clinical application. *Laryngoscope*. 1999;109(S91):1-17.
51. Pathak S, Goldofsky E, Vivas EX, Bonagura VR, Vambutas A. IL-1β is overexpressed and aberrantly regulated in corticosteroid nonresponders with autoimmune inner ear disease. *J Immunol*. 2011;186(3):1870-1879.
52. Vambutas A, Pathak S. Monocytes, macrophages, and microglia and the role of IL-1 in autoimmune inner ear disease (AIED). *Curr Otorhinolaryngol Rep*. 2018;6(2):203-208.
53. Dhimolea E. Canakinumab. *MAbs*. 2010;2(1):3-13.
54. Aftab S, Semaan MT, Murray GS, Megerian CA. Cochlear implantation outcomes in patients with autoimmune and immune-mediated inner ear disease. *Otol Neurotol*. 2010;31(8):1337-1342.
55. Kohlert S, Bromwich M. Mobile tablet audiometry in fluctuating autoimmune ear disease. *J Otolaryngol – Head Neck Surg*. 2017;46(1):18.

How to cite this article: Breslin NK, Varadarajan VV, Sobel ES, Haberman RS. Autoimmune inner ear disease: A systematic review of management. *Laryngoscope Investigative Otolaryngology*. 2020;5:1217–1226. https://doi.org/10.1002/lio2.508