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Immunosuppressive therapy for autoimmune inner ear disease

Maria C Buniel[1,*], **Katie Geelan-Hansen**[1,*], **Peter C Weber**[1], and **Vincent K Tuohy**[1]

[1] Cleveland Clinic, Lerner Research Institute, Department of Immunology, NB30, 9500 Euclid Avenue, Cleveland, OH 44195, USA, Tel.: +1 216 445 9684, Fax: +1 216 444 8372, tuohyv@ccf.org

Abstract

Autoimmune inner ear disease (AIED) is a rare disease that is diagnosed after clinical suspicion and response to corticosteroids. AIED manifests as progressive, bilateral, although often asynchronous, sensorineural hearing loss and can be associated with vestibular symptoms. Since its description as a defined disease entity in 1979, the initial mainstay of treatment remains high-dose corticosteroids. Several animal models have been developed to assist in determining efficacy of immunosuppression in AIED, and several clinical studies have also investigated the role of both steroid and steroid-sparing treatments. Here we discuss the basic science and clinical research surrounding the history of immunosuppressive therapy in AIED.

Keywords

autoimmunity; corticosteroid; hearing loss; immunomodulation; immunosuppression

Autoimmune inner ear disease (AIED) was first described by McCabe in 1979 [1]. AIED is one of the few treatable forms of sensorineural hearing loss and is diagnosed on clinical suspicion. Autoimmune sensorineural hearing loss is characterized by bilateral disease, often with the severity of hearing loss being asymmetric. In McCabe's initial report, hearing loss was slowly progressive and nonfluctuating, worsening over the course of weeks to months. Some cases were associated with temporary facial paralysis and tissue destruction. However, vertiginous episodes were rarely observed. A lymphocyte-migration inhibition assay was the only laboratory test available and assessed the ability of inner ear homogenate to inhibit migration of the patient's peripheral blood mononuclear cells (PBMCs). Most importantly, the auditory symptoms responded to immunosuppressive therapy. McCabe's report summarized data from 18 patients seen and treated over the course of 10 years.

In 1984, Hughes and colleagues published a clinical profile for autoimmune hearing loss developed from 15 patients with laboratory-suggested AIED [2]. In addition to McCabe's observations, Hughes concluded that AIED may present as a localized primary disease or be present in association with a systemic autoimmune disorder, being referred to as secondary. Approximately 30% of patients with AIED have a systemic autoimmune disease [3]. In contrast to McCabe's initial report, Hughes concluded that hearing loss could begin abruptly, fluctuate over time, and occur with or without vertigo.

As reviewed by Hughes and colleagues, treatment at the time was guided by both the experience of the clinician and theoretical management of active autoimmune response [2,4].

Correspondence to: Vincent K Tuohy.

[*]Authors contributed equally to this work as co-first authors

Glucocorticoids were, and still remain to be, the first-line therapy for AIED. Those who failed glucocorticoid therapy were then offered other immunosuppressive agents, with plasmaphoresis being reserved for the most resistant cases. In the three decades since the first report of autoimmune hearing loss, research on the molecular mechanisms underlying this disease and investigation of treatment efficacy have advanced clinical understanding and practice. Our goal here is to provide an overview of the numerous studies that have evaluated the effectiveness of therapies used to treat AIED in both animal models and humans.

Experimental AIED

The features of the various animal models used in AIED research are summarized in Table 1. Initial studies by Harris and colleagues were designed primarily to characterize the immunologic function and immunopriviliged status of the inner ear. To determine if an inner ear immune response was possible, guinea pigs were systemically immunized with keyhole limpet hemocyanin (KLH) and subsequently challenged with an infusion of KLH into the cochlea. These investigators found KLH antibodies in the guinea pig perilymph and showed that the antibodies were produced locally as a result of an accumulation of immunocompetent cells capable of local antigen presentation and antibody production [5–7]. Studies performed by Ma and colleagues further characterized the cellular damage occurring within the guinea pig cochlea following systemic KLH immunization and subsequent local challenge [8]. After cochlear infusion of KLH, these investigators observed inflammatory cells within the cochlea and the location of the inflammatory infiltrates coincided with the destruction of sensory and supporting cells in the surrounding area. Immunized guinea pigs showing severe destruction of the organ of Corti also exhibited profound hearing loss. These studies by Harris and colleagues characterizing the initial animal models of AIED often referred to AIED as sterile labyrinthitis.

C3H/*lpr* and MRL/*lpr* mice are widely used for studying spontaneous systemic lupus erythematosus (SLE) and have also been used to study AIED. Both mouse strains express the lymphoproliferation (*lpr*) mutation of the *fas* gene that results in systemic apoptotic deficiency, prominent lymphoproliferative disorders, and global autoimmune disease when autoreactive T cells fail to undergo Fas-mediated apoptotic death [9]. The phenotype of mice with the *lpr* mutation is further characterized by increased circulating antigen–antibody complexes, anti-DNA antibodies, and a predisposition for lymphoproliferative disease. SLE disease onset in these mice is accompanied by severe hearing loss associated with degeneration of the stria vascularis [10] and immunoglobulin deposition in strial blood vessels [11]. However, despite the severe hearing loss seen in the MRL/*lpr* mice, the sensory structures of the organ of Corti are spared. Furthermore, Ruckenstein and colleagues demonstrated that hearing loss was associated with a loss of endocochlear potential in MRL/*lpr* mouse model [12]. This electrochemical gradient within the cochlea is created and maintained by the vasculature and supportive cells within the stria, and it is this gradient that drives action potential generation in the neurosensory cells of the cochlea. This study provided a distinct physiologic mechanism underlying auditory dysfunction in MRL/*lpr* mice. SLE is predominantly a rheumatologic disease of the microvasculature, so it seems likely that cochlear manifestations of SLE may predominantly involve targeting of small blood vessels rather than other cochlear structures such as hair cells. In summary, investigations using *lpr* mice have provided substantial insights into how AIED occurs as a secondary manifestation of systemic autoimmune disease that involves hearing loss as one of several sequelae resulting from a core global autoimmune abnormality.

Other animal models for AIED have been created by immunizing the host against inner ear homogenate [13–16]. Despite the similar methods used to generate autoimmune hearing loss in each study, the severity of hearing loss and cochlear inflammation varied considerably

[17]. Furthermore, not all animals immunized with inner ear homogenate showed auditory threshold shifts [13,14]. Despite the variable results of these studies involving homogenate immunization, Gloddek and colleagues were able to generate an inner ear autoreactive T-cell line by immunizing Lewis rats with porcine inner ear homogenate [18]. Passive transfer of these T cells to naive animals resulted in labyrinthitis. A similar study was also performed by Tomiyama and colleagues who created labyrinthitis in C57BL/6Cr mice after immunization with bovine inner ear homogenate [16]. These investigators subsequently showed that intravenous transfer of mononuclear cells isolated from the blood, spleen and lymphnodes of homogenate immunized donors triggered an inner ear autoimmune response in naive recipient mice [19]. It is important to note that despite the successful induction of AIED in animals, the use of inner ear homogenate in the above studies precluded identification of the inner ear antigen(s) responsible for AIED induction.

More recently, Solares and colleagues developed a form of primary AIED by immunization of SWXJ mice with recombinant mouse cochlin, an extracellular matrix protein highly and specifically expressed in the inner ear [20,21]. Lymph node cells from mice immunized with cochlin showed robust proliferative responses and increased production of IFN-γ when challenged with the priming cochlin antigen. Moreover, mice immunized with cochlin showed elevated auditory thresholds and cochlear inflammation, and this form of primary AIED could be passively transferred into naive recipient mice by $CD4^+$ T cells. Subsequent studies by Baek and colleagues showed elevated levels of cochlin antibodies and increased frequencies of cochlin specific IFNγ-producing T cells in the PBMCs of primary AIED patients [22]. These studies are the first to provide definitive evidence implicating primary AIED with an adaptive immune response to an inner ear-specific target antigen.

Systemic therapy

Animal models

The treatment of AIED relies heavily on modulation of the immune response. One of the defining characteristics of AIED first described by McCabe was improvement of symptoms following treatment with glucocorticoids [1]. For the past three decades, glucocorticoids have remained the mainstay of treatment. However, owing to the systemic side effects associated with long-term treatment with glucocorticoids, other therapeutic strategies have been explored, such as local application of agents and the use of other immunomodulatory drugs. Several studies have examined the effects of immunomodulatory agents on animal models of AIED. The two most characterized animal models used in these interventional studies are the KLH-induced sterile labyrinthitis guinea pig model and the MRL/*lpr* mouse strain. Animal studies have the advantage of allowing for an in-depth analysis of treatment effects and mechanisms on a functional and cellular level, all of which are inherently much more difficult or impossible to achieve in human studies.

One of the first studies reporting the effects of steroid treatment on an animal model of AIED was published by Ruckenstein and colleagues [23]. These investigators treated MRL/*lpr* mice with dexamethasone injections at 6 weeks of age, long before onset of clinical disease. The mice developed signs of systemic autoimmune disease at 12 weeks and were followed-up to 20 weeks of age. Dexamethasone treatment reduced the degree of uremia, the level of circulating immune complexes, the level of lymphoproliferation, and antibody deposition in the stria. However, based on cochlear histopathology, there were no differences in the level of cochlear disease between the treatment groups. Trune and colleagues tested the effect of prednisolone on MRL/*lpr* mice prior to disease onset [24] and showed results similar to those reported by Ruckenstein and colleagues [23] with little difference in cochlear pathology between prednisolone- and control-treated mice. However, auditory brain stem responses showed that treatment with prednisolone prior to disease onset resulted in preservation of

cochlear function. Similarly, Trune and colleagues also found that MRL/*lpr* mice had lower auditory thresholds when prednisolone treatment was initiated in the drinking water after onset of hearing loss and that treated mice showed a significantly slower rate of declining auditory function over time [25].

The mechanism of action of corticosteroid therapy in AIED is somewhat controversial. The anti-inflammatory and immunosuppressive effects of glucocorticoids are well established. However, glucocorticoids are also capable of binding mineralocorticoid receptors [26], and may possibly mediate therapy in AIED by regulating inner ear electrolyte balance. To address this issue, Trune and colleagues compared aldosterone and prednisolone treatment of MRL/*lpr* mice after onset of systemic disease and found that aldosterone was equivalent to prednisolone in reversing hearing loss [27]. Moreover, the morphology of the stria vascularis returned to normal in aldosterone-treated mice whereas marked edema and vessel wall thickening occurred in the prednisolone-treated mice. In addition, the therapeutic effect of aldosterone treatment was blocked by spironolactone, a mineralocorticoid-receptor antagonist [28]. Thus, considering the alteration in endocochlear potential observed concomitantly with hearing loss in AIED, it seems likely that glucocorticoid therapy in AIED may be due, in part, to restoration of the inner ear electrochemical gradient through mineralcorticoid-receptor signaling. However, in a follow-up study, aldosterone did not have an effect on the level of circulating antibody complexes, which were reduced in MRL/*lpr* mice treated with prednisolone [29]. Thus, it seems reasonable that prednisolone-mediated therapy in AIED may also be due to immunosuppression and reduction of the levels of circulating antibody complexes. These findings have substantial clinical significance for the development of future treatments for AIED.

Other immunomodulatory agents have been examined for treatment of autoimmune hearing loss as a result of the systemic side effects associated with long-term steroid use. The most researched nonsteroidal agents in animal models are inhibitors of TNF-α. Upon binding to its receptor, TNF-α triggers expression of cell adhesion molecules on vascular endothelial cells, thus facilitating extravasation of leukocytes and monocytes to the targeted area of inflammation. As a result, TNF-α is essential for amplification of the adaptive immune response, and TNF-α antagonists are currently used as adjunct therapy in conjunction with steroids for treatment of autoimmune diseases [30]. Similar to the studies of glucocorticoid treatment on experimental models of AIED, interventional studies using TNF-α antagonists allow for correlation of auditory function with histologic examination.

The importance of TNF-α in the KLH model of AIED was established by Satoh and colleagues who showed that TNF-α was the first cytokine to be expressed by inner ear infiltrating cells following systemic KLH immunization and KLH infusion into the cochlea [31]. These investigators also showed that TNF-α antagonism following treatment with etanercept (Enbrel®), a recombinant human fusion protein in which the Fc of IgG_1 is linked to the soluble TNF receptor [32], reduced cellular infiltration and cochlear fibrosis compared with controls. In a subsequent study, these same investigators also found that the cells within the endolymphatic sac are required for developing an adaptive immune response in the KLH labyrinthitis model of AIED, and that these cells are a source of TNF-α needed for amplification of the immune response [33]. Wang and colleagues found that intraperitoneal injection of etancercept was also effective in reducing cochlear inflammation and hearing loss in the KLH labyrinthitis model [34].

The only comparative study of systemic treatments for autoimmune hearing loss in an animal model was performed by Lobo and colleagues who used the KLH labyrinthitis model to compare the effectiveness of systemic methylprednisolone and etanercept in preventing hearing loss [35]. Animals were administered either methylprednisolone or etanercept 30 min

before KLH infusion and 3 days after. Treatment with methylprednisolone and etanercept resulted in significantly lower auditory threshold shifts (41.5 and 37.5 dB, respectively) compared with a 60 dB threshold shift in sham-treated control guinea pigs. Since the threshold shifts for each treatment were not significantly different from each other, these investigators concluded that etanercept and methylprednisolone were equally effective in preventing hearing loss in the KLH labyrinthitis model. This study did not include a treatment group who received both methylprednisolone and etanercept; therefore, no conclusions can be drawn regarding the effectiveness of an etanercept/methylprednisolone combination therapy.

Human clinical studies

The classic description of AIED by McCabe includes responsiveness to immunosuppression [1]. Although McCabe stressed the use of cyclophosphamide 60 mg (2 mg/kg) twice daily and prednisolone 30 mg every other day, the most common initial treatment involves high-dose corticosteroids [36,37]. General treatment recommendations include either prednisone 60 mg/day or 1 mg/kg/day for 2–4 weeks [38–42]. Prompt treatment of AIED is recommended since irreversible damage may occur within 3 months, although recovery of useful hearing has been observed after a treatment delay of 2 months [2,39]. Treatment duration may also affect outcome since AIED may require 4 weeks of high-dose corticosteroids before a significant response occurs [39]. By contrast, 1 year of immunosuppressive treatment after the disappearance of active disease is recommended for other autoimmune types of vasculitis [43].

Treatment as outlined by Rahman and colleagues includes sodium restriction, a thiazide diuretic and high-dose prednisone for 2 weeks, followed by assessment with audiogram [39]. These investigators defined a positive response as a 15-dB increase in hearing at one frequency, 10 dB at two or more consecutive frequencies or a 15% increased word discrimination score. If progressive hearing loss or a lack of improvement manifests, then an additional 2 weeks of prednisone or intratympanic dexamethasone may be considered. If there is still no response after 4 weeks of high-dose corticosteroids, corticosteroids are rapidly tapered and no further immunosuppressive regimen is recommended. No additional immunosuppression is considered if hearing remains stable during steroid taper and after cessation of treatment or if a patient can be maintained on low-dose prednisone. The subset of patients who require high-dose corticosteroids to maintain hearing are considered for adjunct immunosuppressive therapy in order to avoid the side effects of corticosteroids [39].

A retrospective review of 42 patients with AIED by Broughton and colleagues found 78.6% (33 of 42) of patients were treated with corticosteroids and that 70% (23 of 33) patients improved while 30% (ten of 33) of patients were unresponsive to treatment [40]. In this study, clinical response was defined as a 10 dB average improvement in pure tone threshold at 500/1000/2000 Hz, and/or a 12% improvement in speech discrimination score. Of the patients that received follow-up audiometry (35 of 42) at a mean of 34.4 (1–132) months, 14% (five of 35) demonstrated improvement based on the study's criteria. However, it is not clear if these 35 patients were part of the group initially treated with corticosteroids (33 of 42). These investigators concluded that treatment of AIED requires high-dose prednisone (1 mg/kg/day) for 4 weeks followed by a taper to the lowest possible dose required to treat hearing symptoms with repeated courses of high-dose prednisone reserved for disease fluctuations. Additional studies involving AIED patients treated with high-dose prednisone (1 mg/kg/day, maximum dose of 60mg/day or other steroid dose equivalent) reported a 44% (28 of 63) response rate after a minimum treatment of 7 days [41] and a 53% (31 of 58) response rate after a 4-week treatment course [44].

Use of other immunomodulators to maintain improvements in steroid-responsive patients is advocated to reduce the side effects of long-term corticosteroids. Initial reports of methotrexate in this role were promising [43,45–47]. However, a randomized double-blind, placebo-controlled trial of steroid-responsive patients with AIED found that methotrexate was no more effective than placebo in maintaining hearing improvement [48]. Etanercept was used in a retrospective review of 12 steroid-responsive patients and it was found that 11 of 12 patients had improvement or stabilization of hearing and tinnitus. Of eight patients with vertigo, seven showed improvement [49]. In another study, 23 steroid-responsive patients, ten of whom were on long-term prednisone, started treatment with etanercept 25 mg twice-weekly with tapering of steroids, and 30% of the etanercept-treated patients showed improved hearing [50]. Three of the ten patients on long-term prednisone were able to discontinue corticosteroid treatment without a change in their hearing, and on average, patients were able to decrease their daily prednisone dose by 19%. Further evaluation of etanercept includes a study of 20 steroid-responsive AIED patients randomized to treatment with either etanercept 25 mg twice weekly or placebo [51]. Patients continued treatment on their baseline immunosuppressant during the 8 weeks of treatment and 4 weeks of follow-up. There were no significant differences in hearing, tinnitus or vertigo in patients treated with etanercept compared with placebo [51]. A subgroup of patients may benefit from cyclophosphamide therapy [42], although other studies have found little benefit [40,52]. Clearly, the potential gains must outweigh the inherent toxicity risks in use of cyclophosphamide for AIED.

Some studies have included azathioprine and prednisone or mycophenolate mofetil and prednisone or combination cytotoxic agents as possible treatment options, but controlled studies have yet to be conducted with these treatment modalities [40,52–54]. Other treatment options have included plasmapheresis. In a long-term study of AIED patients who had been treated with plasmapheresis, 50% of patients showed improved or stable hearing at a 6.7-year follow-up assessment and 25% required immunosuppressive therapy [55].

Intratympanic therapy

Intratympanic treatments for AIED have increased in clinical use in order to prevent the side effects associated with systemic therapy. The pharmacokinetic profile of glucocorticoids using an intratympanic route has been described by several studies showing the feasibility of this method for treatment delivery (Box 1) [56–60]. Yang and colleagues showed no histologic or hearing improvement following intratympanic injection of dexamethasone, cyclosporine, prednisolone, fluorouracil or FK506 (tacrolimus) in the sterile labyrinthitis guinea pig model, and concluded that the negative results may have been due to the rapid clearance of each drug from the perilymph within hours, while KLH persists in the perilymph for up to 2 weeks [61]. These investigators proposed that additional studies involving other models, different drugs, varying dosages and alternative timing protocols be performed. Indeed, a subsequent study by these same investigators showed attenuation of hearing loss in the KLH labyrinthitis model following intratympanic injection of the TNF-α antagonist etanercept [34]. More recently, Barkdull and colleagues found that intratympanic injection of AM-111, an inhibitor of c-Jun N-terminal kinase (JNK)-mediated apoptosis and inflammation, decreased threshold shifts and cochlear inflammation in the KLH labyrinthitis model [62]. This promising outcome provides further support for the role of TNF-α in AIED since TNF-α binding triggers the JNK signaling cascade predominantly amplified in the adaptive immune response.

Box 1

Pharmacokinetics of glucocorticoids in the inner ear

- As reviewed by Goycoolea, the round window consists of an outer epithelium layer, an inner layer of connective tissue, and an inner epithelium layer [56]. This

three-layer structure is thought to be more permeable to substances compared with the blood–labyrinth barrier. Similar to the blood–brain barrier, the blood–labyrinth barrier is a selectively permeable membrane that serves to maintain the electrochemical gradients unique to the perilymph. The round window transduces the mechanical energy of sound conducted through the middle ear into the scala tympani of the inner ear and facilitates the secretion and absorption of substances to and from the perilymph. The permeability of the round window has been characterized in several studies reviewed recently [56]. Permeability of substances depends on size and electrical charge of the substance, as well as the thickness of the round window membrane. Permeability of substances can also be affected by the presence of facilitating agents, such as histamine.

- Local application of glucocorticoids and other therapeutic agents into the inner ear has increased in clinical use. The premise underlying local application is to prevent unwanted side effects typically associated with systemic administration of glucocorticoids and other immunomodulatory agents. In clinical practice, therapeutic agents are delivered to the inner ear by intratympanic injections into the middle ear. In theory, local application into the middle ear would allow these substances to diffuse through the round window to the inner ear.
- To determine the effectiveness of intratympanic injections as a method for successful drug delivery to the inner ear, Parnes and colleagues investigated the pharmacokinetics of hydrocortisone, methylprednisolone and dexamethasone in the inner ear following oral, intravenous and intratympanic administration [57]. They were able to show that intratympanic injections provided the highest inner ear concentrations of all three drugs and found that methylprednisolone achieved the highest concentration for the longest duration within the perilymph, when compared with hydrocortisone and dexamethasone (when adjusted for anti-inflammatory equivalency). Subsequently, Chandrasekhar and colleagues examined the effects of facilitating agents on the pharmacokinetics of intratympanic steroid injections and found that the use of histamine as a facilitator significantly raised the concentration of dexamethasone within the perilymph compared with intratympanic dexamethasone alone [58]. In addition, these investigators found that based on plasma levels, intratympanic dexamethasone injections did not result in significant systemic absorption. Similar results were obtained by others measuring perilymph steroid concentrations following systemic versus local administration [59,60]. Collectively, these pharmacokinetic studies show that the limited permeability of the blood–labyrinth barrier prevents systemic absorption of medications delivered to the inner ear by intratympanic injections and that the unique properties of the round window can be exploited for effective targeted drug delivery to the inner ear.

Clinical studies of intratympanic steroids for the treatment of AIED are few. In a study involving 46 patients with various types of inner ear disease treated with intratympanic steroids, five were considered to have AIED [63]. Four of the five patients with AIED treated with intratympanic steroids showed improvement in their speech discrimination score ranging from 8 to 20%, with minimal changes in speech reception thresholds and no report on pure tone audiometry changes. Another study involving 37 patients with new-onset sensorineural hearing loss of varying etiologies reported clinical findings following intratympanic steroid treatment [57]. Within this cohort, one patient was considered to have AIED. This patient presented with profound sensorineural hearing loss in the right ear and a 30-dB hearing loss in the left ear. Initial systemic steroid treatment resulted in improvement of hearing loss in the left ear, which worsened when steroid taper was attempted. Owing to unwanted side effects related to systemic

steroids, the patient elected to try intratympanic steroid injections. While this AIED patient experienced multiple relapse episodes, the investigators reported the success of intratympanic steroids at treating the hearing loss during these episodes. The details of this case report demonstrate the promise of intratympanic steroids as a successful therapeutic intervention for AIED [57].

Although response to immunosuppression is part of the diagnosis of AIED, one retrospective study examined 16 patients who responded poorly to corticosteroid treatment or showed recurrences with low-dose methotrexate and/or intratympanic steroids [64]. In this study, methotrexate was offered to these patients at a dose of 15 mg/week. If the patient refused methotrexate treatment or if methotrexate therapy failed (as evidence of no response or hearing loss relapse), then they were offered two intratympanic injections of methylprednisolone 0.3–0.5 ml at 40 mg/ml given 1 week apart. Eight patients chose local treatment, five chose methotrexate, and three were treated with both methotrexate and intratympanic methylprednisolone. In patients treated with methotrexate alone, five of ten ears had stable hearing, four of ten ears had worse hearing, and one of ten ears had improved hearing. All five patients treated with methotrexate alone noted an improvement in vestibular symptoms. Five of eight patients treated with intratympanic methylprednisolone had improved hearing, one of eight had unchanged hearing, and two of eight had worse hearing. All seven patients who reported vestibular symptoms in this group had improvement of those symptoms. Out of three patients treated with both methotrexate and intratympanic methylprednisolone, two had unchanged hearing while one out of three had improved hearing. One patient with vestibular symptoms at baseline experienced improvement in these symptoms. Thus, this study provides additional evidence for use of intratympanic steroids as a potential, first-line option for refractory AIED, allowing patients to be spared the risk associated with cytotoxic therapies reserved for those failing systemic steroids.

Local perfusion of infliximab, a humanized TNF-α monoclonal antibody, has also been evaluated in patients with AIED [65]. Nine patients were treated in two groups; group 1 was initially treated with methylprednisolone 32 mg for 1 week, followed by a 2-week taper, and group 2 began weekly local infliximab treatments for 4 weeks after completion of initial corticosteroid treatment and after reoccurrence of hearing loss. No further systemic corticosteroids were prescribed for group 2. In group 1, pure tone average increased by 11.6 dB during the steroid taper, and the patients immediately resumed methylprednisolone 32 mg daily and local perfusion of infliximab began. Four of five patients in this group were able to be tapered off the corticosteroids in 3 weeks without a decline in hearing. Hearing remained stable in the four responders for an average of 17 weeks (range 10–38 weeks). One patient had a recurrence of hearing loss after 1 month and was treated with local infliximab with success. Three of four patients in group 2 had an average improvement in pure tone average of 22.6 dB, while one patient did not show any improvement in hearing. Hearing remained stable for an average of 22 weeks (range 10–38 weeks) for the three responders. One patient had a recurrence of hearing loss 1 week after completion of infliximab, and this patient was successfully treated with another local application of infliximab. This pilot study describes the efficacy of intratympanic application of infliximab for treatment of AIED by allowing for steroid taper and facilitating hearing improvement.

Conclusion & future perspective

Despite numerous clinical and animal studies, the treatment recommendation for AIED remains high-dose systemic corticosteroids. Advances in research and treatment are complicated by the unknown pathophysiology of AIED and the lack of a reliable diagnostic test. It is difficult to study a clinically diagnosed disease when there are probably many different etiologies causing similar presenting symptoms and a response to corticosteroids. There is yet

to be an analogous animal model to this human disease, largely because this human disease has yet to be clarified and may involve several underlying immune processes. Another complicating factor is that AIED is a relatively rare disorder that precludes the examination of large patient numbers in clinical trials. Other difficulties with clinical research include nonuniform criteria for hearing improvement and subjective improvement in hearing often poorly correlates with objective evaluations [3]. A recent study on the audiometric changes in patients with AIED who responded to treatment may now provide guidelines for clinical response [66]. In addition, few studies include vestibular symptoms and their changes with treatment in the outcomes.

Further research in AIED may focus on elucidating the etiology of the disease and distinguishing primary AIED from secondary AIED. Advances in the development of diagnostic tests and the role of immunologic testing in this disease are also gains that are reachable in the near term. Appropriate treatment of AIED may provide reversal of sensorineural hearing loss and may best be served by exploring new treatment modalities, focusing on intratympanic delivery. Optimization of dosage and frequencies as well as long-term effects of intratympanic delivery can be further examined in the treatment of AIED.

Executive summary

Introduction

- Autoimmune inner ear disease (AIED) is a reversible form of sensorineural hearing loss when immunosuppressive treatment is given.
- AIED is described as progressive, bilateral although asymmetric sensorineural hearing loss that responds to treatment with corticosteroids.
- Primary AIED exists in the absence of systemic disease and is probably an inner ear-specific autoimmune disease involving T-cell targeting of inner ear-specific antigens such as cochlin.
- Secondary AIED may be the consequence of systemic immune abnormalities that involve the inner ear.

Systemic treatment

- Corticosteroids administered prior to development of AIED in mice lead to retained cochlear function, although no changes in cochlear histopathology could be noted.
- High-dose corticosteroids for 2–4 weeks are recommended for patients with suspected AIED.
- Treatment with low-dose methotrexate was not found to be efficacious in AIED.
- Animal models with keyhole limpet hemocyanin-induced labyrinthitis treated with etanercept, a TNF-α inhibitor, found decreased cochlear inflammation with reduction of hearing loss.
- Clinical studies on treatment of AIED with etanercept are mixed but promising, and a randomized controlled trial has yet to be conducted.
- Treatment with cyclophosphamide remains an option, but toxic risks often deter clinicians and patients from its use.
- Other treatment options include combination cytotoxic agents and plasmapheresis for potential use in patients with AIED.

Intratympanic treatment

- In animal models, it was found that medications can be delivered to the inner ear through the round window and intratympanic administration.
- Intratympanic steroids for treatment of AIED have produced mixed results.
- Intratympanic injection of infliximab, a humanized TNF-α monoclonal antibody, may provide a steroid-sparing treatment option.

Conclusion & future perspective

- Pathophysiology of AIED is largely unknown and is an area for future research.
- AIED remains a clinically diagnosed entity, development of a diagnostic test remains a challenge for the future.
- Treatment with nonsteroidal medications has yet to be identified.

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Table 1

Animal models used in autoimmune inner ear disease research.

Animal models of AIED	Description of each animal model	Histopathology findings	Ref.
The KLH labyrinthitis model of AIED	Guinea pigs are systemically immunized with KLH, followed by infusion of KLH into the cochlea. KLH infusion causes an influx of immunocompetent cells and leads to the production of KLH antibodies, which are detected in the perilymph	Inflammatory infiltrates with destruction of sensory and supporting cells within the cochlea	[5–8]
C3H/*lpr* and MRL/*lpr* mouse strains	Mouse strains widely used for studying SLE and AIED. Both strains express the *lpr* mutation of the *fas* gene resulting in systemic apoptotic deficiency. This phenotype is associated with lymphoproliferative disorders and global autoimmune abnormalities	Degeneration of stria vascularis with immunoglobulin deposition in strial blood vessels; organ of Corti is spared	[10–12]
Immunization with inner ear homogenate*	Guinea pigs are immunized with bovine or guinea pig inner ear homogenate	Variable findings; from near normal to loss of cochlear neurons, edema, hemorhage and perivascular inflammatory infiltrate	[13–14]
Immunization with cochlin peptides‡	SWXJ mice are immunized with immunogenic peptides derived from mouse cochlin, the most abundant protein expressed in the inner ear. Hearing loss develops in mice that passively receive cochlin-specific $CD4^+$ T cells from immunized donors	Prominent spiral ligament inflammation	[20]

*Hearing loss was only observed in 20–30% of ears studied.

‡Severe AIED may also be transferred by T cells from mice immunized with recombinant human cochlin. AIED: Autoimmune inner ear disease; KLH: Keyhole limpet hemocyanin; SLE: Systemic lupus erythmatosus.