Chapter 10
Anti-inflammatory Therapies for Sensorineural Hearing Loss

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Abstract Anti-inflammatory and immunosuppressive therapies have been widely employed in the treatment of sensorineural hearing loss in the context of autoimmune inner ear disease (AIED) and idiopathic sudden sensorineural hearing loss (ISSHL). While steroids are the mainstay of treatment for these disorders, numerous other therapies, including cyclophosphamide, methotrexate, azathioprine, rituximab, anakinra, anti- TNF-α agents, and plasmapharesis have been investigated. Here we will describe the most commonly-studied of these immune-modulating therapies and review the evidence for their efficacy in the treatment of inner ear disorders, focusing on AIED and ISSHL. Further investigation of the potential inflammatory mechanisms mediating these forms of sensorineural hearing loss may ultimately identify targets for future treatments.

Keywords Sensorineural hearing loss · Autoimmune inner ear disease · Corticosteroids · Immunomodulation · Sudden hearing loss

1 Introduction

The role of inflammatory mechanisms in the pathogenesis of sensorineural hearing loss (SNHL) holds great interest for researchers as it suggests the possibility of reversing hearing loss through the use of anti-inflammatory or immunosuppressive medical therapies. Corticosteroids, in particular, have been employed in the treatment of hearing loss since the 1950s with varying degrees of success, and their effectiveness in certain cases has been used as evidence of an underlying immune-mediated mechanism (Trune and Canlon 2012). One entity, autoimmune inner ear disease (AIED), has been partially defined by its response to immunosuppressive medications (McCabe 1979). However, immunosuppressive therapies have also been used in other conditions including idiopathic sudden sensorineural hearing

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loss (ISSHL), Meniere's disease, and SNHL related to systemic autoimmune diseases such as granulomatosis with polyangiitis, systemic lupus erythematous, and Cogan syndrome. Each of these conditions can have considerable overlap in their presentation, may be difficult to distinguish on initial presentation, and may in fact encompass many different disorders with heterogeneous pathologic mechanisms.

This lack of clarity in the underlying inner ear pathophysiology of these diseases makes the directed study of therapeutic options challenging. Indeed, many treatments have been tested empirically on the basis of their efficacy in systemic autoimmune diseases, under the presumption that the SNHL seen in AIED and a least a subset of patients with ISSHL and Meniere's disease is related to an underlying inflammatory or immune-mediated process. In several studies examining the effects of various immunosuppressive medications on hearing loss, patients considered to have Meniere's disease have been included under the umbrella of 'AIED' or been labeled as having 'immune-mediated Meniere's disease' (Matsuoka and Harris 2013; Matteson et al. 2000, 2005). The absence of a definitive diagnostic test, variable presentation, fluctuating course, low incidence, and often spontaneous improvement of hearing in these diseases create additional challenges for study design in this population.

Despite an extensive body of literature examining the use of steroids in hearing loss, our understanding of the primary mechanisms through which steroids act in the inner ear is limited. Steroids have become first-line therapy for both AIED and ISSHL although the optimal choice of drug, dose, and route are debated. Many other immunosuppressive therapies have been studied in the treatment of AIED, though these studies tend to be retrospective or observational in nature and are limited by small sample sizes. The clinician must therefore balance the potential benefits against the considerable risk of side effects from these therapies. This chapter will review the role of anti-inflammatory and immunosuppressive therapies in various inner ear disorders, with a particular focus on AIED and ISSHL.

2 Autoimmune Inner Ear Disease

Steroids in Autoimmune Inner Ear Disease

Corticosteroids are a class of molecule with a wide array of effects in nearly every organ system. Upon binding to the glucocorticoid receptor, a member of the nuclear receptor family, they allow translocation of the receptor to the cell nucleus, where they regulate transcription of corticosteroid-responsive genes. Signaling through this pathway leads to apoptosis of inflammatory cells and suppression of expression of the proinflammatory cytokine tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) expression, among other effects (Flammer and Rogatsky 2011). Steroids have been the primary therapy for AIED ever since McCabe first described, in 1979, a series of patients with an unusual form progressive, bilateral sensorineural hearing loss which he postulated was autoimmune in etiology and which responded to

treatment with dexamethasone and cyclophosphamide (McCabe 1979). Indeed, response to steroids has been used as a diagnostic criterion for AIED, as no single definitive diagnostic test exists (García-Berrocal et al. 2003). Since McCabe's study, numerous case series and animal studies have emerged to evaluate the efficacy of steroids in AIED, develop treatment algorithms, and elucidate the mechanisms underlying the steroid response in AIED.

Animal Studies

Despite their effectiveness in reversing hearing loss related to AIED, the actions of steroids in the inner ear are unclear. Animal models have therefore proven useful not only in investigating the pathogenesis of AIED but also in revealing potential pathways through which steroids may exert their effects. One such model is the MRL-Fas^{lpr} mouse, which carries a mutation in the *Fas* gene that prevents apoptosis of self-recognizing T lymphocytes. These mice develop a systemic autoimmune disease similar to systemic lupus erythematous as well as elevated auditory brainstem response (ABR) thresholds and pathologic changes within the stria vascularis, which is responsible for maintaining the endocochlear potential; these changes include intracellular edema, cellular degeneration and intra-capillary antibody deposition (Ruckenstein et al. 2009; Ruckenstein and Hu 1999).

Trune et al. demonstrated that administration of oral prednisolone in MRL-Fas^{lpr} mice prior to the onset of systemic autoimmune disease and hearing loss could prevent hearing loss in treated animals compared to untreated controls (Trune et al. 1999a). Moreover, a companion study showed that when prednisolone was administered after the onset of clinical disease, ABR thresholds stabilized or improved in 53% of mice as compared to 25% in untreated controls (Trune et al. 1999b). Ruckenstein et al. investigated the pathogenesis of strial disease in AIED by treating MRL-Fas^{lpr} mice with dexamethasone beginning at 6 weeks of age, before autoimmune disease onset, and examined inner ear histology in animals sacrificed at 20 weeks (Ruckenstein et al. 1999). The authors found that dexamethasone administration reduced serum immunoglobulin levels, decreased lymphoid hyperplasia, improved renal function, and prevented antibody deposition in the stria vascularis of treated mice. However, steroid-treated mice still developed strial cellular edema and degeneration similar to mice that were untreated, suggesting that, while steroids were able to eliminate antibody deposition, strial degeneration was mediated through another process.

Though steroids' improvement of cochlear dysfunction in AIED has often been ascribed to inhibition of the immune-mediated inflammatory response, glucocorticoids can also bind to mineralocorticoid receptors expressed in the inner ear and thereby influence ion transport (Trune and Canlon 2012). Trune et al. have hypothesized that corticosteroids, by acting on mineralocorticoid receptors, may reverse hearing loss in AIED by restoring ion homeostasis in the stria vascularis (Trune et al. 2006). Using the MRL-Fas^{lpr} mouse model for autoimmune SNHL, the authors

tested hearing in mice treated with either aldosterone, a mineralocorticoid, or prednisolone (Ruckenstein 2004). Mice treated with aldosterone experienced similar hearing improvement to those given prednisolone. Examination of stria vascularis morphology of mice in the aldosterone treatment group revealed a reversal of the edema and degeneration seen in the untreated mice. Mice in the prednisolone group showed some improvement in the appearance of the stria, though not to the same degree as in the aldosterone group. A follow-up study demonstrated that mice treated with prednisolone and spironolactone, a mineralocorticoid receptor antagonist, had a hearing decline similar to mice who were not treated at all, suggesting that prednisolone's hearing effects in this mouse model were mediated through its action on the mineralocorticoid receptor (Trune et al. 2006). While these studies point to an interesting means by which steroids can reverse inner ear damage, whether or not the mouse model accurately reflects the true pathogenic events of AIED in human populations is unknown.

Human Studies

An early report of AIED treatment in human subjects emerged in 1984, when Hughes et al. reviewed the clinical experience with AIED at their institution (Hughes et al. 1984). The authors advocated initiating treatment with high-dose, short-term prednisone, followed by a lower maintenance dose over a subsequent period of weeks to months, reserving cytotoxic medications for those patients who did not respond to steroids. They noted that response time to treatment was variable, ranging from rapid recovery within weeks to a delayed recovery of hearing over the course of months. While no prospective, randomized clinical trials have compared the efficacy of various steroid doses, routes of administration, and duration of treatment, initial treatment with oral prednisone 1 mg/kg/day or 60 mg for a period of 4 weeks has come to be most commonly used (Broughton et al. 2004; Niparko et al. 2005; Ryan et al. 2009; Ruckenstein 2004). Hearing is tested at the start of treatment and at the end of 4 weeks. Various criteria have been used to define who is a steroid-responder, for example: if pure-tone thresholds improve by at least 15 dB at one frequency or 10 dB at two or more consecutive frequencies; if speech discrimination scores improve by 12%; if the average (PTA) threshold improves by 10 dB (Broughton et al. 2004; Niparko et al. 2005). Steroid-responders are then tapered over a variable length of time. If steroid-responders experience a deterioration in hearing after tapering of steroids, they are then restarted on high-dose steroids. Patients who show no response after the initial treatment period, however, are rapidly weaned off and considered for alternative therapies.

Clinical response to steroids is variable. Rauch et al. reported an overall steroid response rate of 60% in patients with AIED treated at their institution, though it is unclear over what length of time this was measured (Rauch 1997). In a cohort of patients with AIED reviewed by Broughton et al., 70% showed an initial response to steroids however the response was often not sustained over the mean follow-up

period of 34.4 months (Broughton et al. 2004). Patients often required a repeat course of high-dose steroids and 71% of initial steroid responders ultimately required treatment with alternative immunosuppressive therapies at some point.

In a prospective study of 116 patients with AIED, Niparko et al. sought to describe with more precision the effect of prednisone treatment on the audiometric profile of patients after 4 weeks of therapy (Niparko et al. 2005). Most subjects experienced improvement in or stabilization of their hearing over that time period. Pure-tone averages (PTA) improved by 1 dB or more in 53.5% of subjects and remained stable in 29% of subjects while mean PTA improved from 52.4 dB to 48.3 dB in the better-hearing ear. Similarly, 59.5% of subjected experienced at least a 2% improvement in speech discrimination, with speech discrimination remaining stable in another 18.1% of subjects. Across all subjects, speech discrimination improved from 71.4 to 78.1% in the better-hearing ear. Loveman et al. reviewed 30 patients with a diagnosis of AIED (Loveman et al. 2004). In their series, the mean initial steroid dose was 35.1 mg and mean initial duration of treatment was 2.2 weeks, with a mean total duration of therapy of 7.3 weeks. Patients who did not respond to treatment were then given a 2- to 3-week course of prednisone at a higher dose of 1 mg/kg/day; steroids were discontinued if they did not respond to this dose, and patients were considered for treatment with methotrexate. Patients who were initial responders to steroids but relapsed after steroids were discontinued were given a second course of therapy at the previously successful dose. Fifty percent of patients in this cohort met criteria for audiometric improvement with steroids, while 12% experienced stable hearing. The authors found that this management strategy, while achieving hearing outcomes consistent with previous reports, resulted in a lower average dose and duration of steroid therapy. They suggest that the commonly recommended initial prednisone dose of 1 mg/kg and treatment duration of 4 weeks may be unnecessary for satisfactory outcomes, though other studies suggest a shorter duration of treatment may place patients at a higher risk of relapse (Rauch 1997).

Corticosteroids can have serious long-term side effects including osteoporosis, hypertension, glaucoma, weight gain, hyperglycemia, and adverse psychological effects, however one prospective, long-term study suggests that they are safe and generally well-tolerated in patients being treated for AIED (Alexander et al. 2009). Alexander et al. analyzed adverse events in 116 patients with AIED who were given high-dose prednisone as part of a prospective trial comparing methotrexate to prednisone treatment (Alexander et al. 2009). Study subjects received prednisone 60 mg/day as part of a 1-month challenge, and those whose hearing improved underwent an 18-week prednisone taper. Subjects were followed for a mean of 66 weeks, with few serious adverse events occurring during that period. A total of 16 patients (14%) experienced adverse events during the initial 1-month prednisone challenge, and 7 patients (6%) were unable to complete 1 month of treatment due to an adverse event. Of patients who completed the full 22-week prednisone course, the most common adverse events were hyperglycemia (17.6%), abdominal pain, shortness of breath, elevated liver function tests, and joint pains (5.9% each). Weight gain was also common. No incidences of osteonecrosis or fractures were reported.

In order to avoid the toxicities of systemic steroids as well as potentially benefit from higher inner ear drug levels, the use of intratympanic (IT) steroids has been investigated (Parnes et al. 1999). One animal study suggested IT steroids were not effective in improving hearing or reducing inner ear inflammatory infiltrates in a guinea pig model of immune-mediated labyrinthitis, and human studies have been limited to small case series (Parnes et al. 1999; Yang et al. 2000; Harris et al. 2013; García-Berrocal et al. 2006). Harris et al. described a series of 4 patients with AIED, of which 3 demonstrated improved hearing after IT steroid injections; however the patients were also receiving other immunosuppressive medications at the same time, including systemic steroids, so it is difficult to determine which, if any, intervention was effective (Harris et al. 2013). A retrospective case series of patients with AIED who were either refractory to or unable to wean from steroids included 11 patients who additionally failed or refused methotrexate therapy and were treated with IT methylprednisolone (García-Berrocal et al. 2006). Patients were given 6-methylprednisolone (0.3–0.5 mL of 40 mg/mL solution), weekly over a period of at least 2 months. Hearing was improved in 6 patients (54.5%) stable in 3 (27.3%), and worse in 2 (18.2%) and vestibular symptoms improved in all affected patients.

Identification of markers of steroid-responsiveness has been an active area of investigation. In 1990, Harris and Sharp detected antibodies to a 68-kD inner ear antigen in patients with suspected immune-mediated hearing loss using Western blot analysis of patient serum (Harris and Sharp 1990). In one series, 89% of patients with idiopathic, bilateral, progressive SNHL had antibodies to this protein and, moreover, 75% of those who were seropositive responded to treatment with prednisone while only 18% of seronegative patients responded (Moscicki et al. 1994). The authors suggested that the presence of these antibodies could therefore be used to predict which patients will have favorable responses to steroids in order to guide treatment decision-making. However, more recent studies have failed to find this correlation between anti-68-kD antibody status and steroid responsiveness (Broughton et al. 2004; Zeitoun et al. 2005). This discrepancy could be explained by the test's high specificity (90%), but low sensitivity (42%) in predicting steroid-responsiveness in a series of patients with suspected AIED; many patients who are antibody-negative will therefore also respond to steroid therapy (Hirose et al. 1999). Zeitoun and colleagues used an immunofluorescence-based assay to detect antibodies against an inner-ear supporting cell antigen in patients with suspected AIED (Zeitoun et al. 2005). Though they found no correlation between steroid-responsiveness and presence of the 68-kD protein based on the Western blot serum analysis as described by Harris and Sharp, they found that the presence of antibodies using the immunofluorescence was significantly associated with steroid-responsiveness. Immunofluorescence-positive patients were almost three times as likely to respond to treatment as those who were negative. The authors suggest that the Western blot test could be detecting other clinically-irrelevant proteins of a similar weight while the immunofluorescence test more specifically targets antibodies with a specific binding pattern on inner ear supporting cells. Therefore this assay may hold value in the future in guiding the use of steroids in patients with AIED.

In addition to specific antibodies, alterations in expression of the cytokine IL-1β and its receptor may be markers for steroid-responsiveness in AIED (Pathak et al. 2011; Vambutas et al. 2009). Recent studies have pointed to a potential role of cytokines in the pathogenesis of AIED, in particular, those in the interleukin-1 (IL-1) family (Pathak et al. 2011; Vambutas et al. 2009). For instance, IL-1β, a proinflammatory cytokine, is expressed by fibrocytes in the spiral ligament and spiral limbus in response to cochlear injury, and expressed by infiltrating inflammatory cells after the introduction of antigen into the cochlea of a systemically sensitized mouse (Satoh et al. 2002). Vambutas et al. examined interleukin 1 Receptor Type II (IL1R2), a protein expressed on the surface of B cells, macrophages, and neutrophils that sequesters IL-1β and thereby inhibits its proinflammatory effects (Vambutas et al. 2009). Expression of IL1R2 is induced by steroids. The authors found that patients with AIED who responded to corticosteroids had peripheral blood mononuclear cells (PBMC) that showed a robust increase in IL1R2 expression in vitro in response to dexamethasone, while PBMCs of steroid non-responders showed minimal increase. In a follow-up study, corticosteroid-responders also had lower circulating plasma levels of IL-1β and their PBMCs showed suppressed transcription of IL-1β in response to dexamethasone in vitro compared to non-responders (Pathak et al. 2011). These studies together suggest a potential method of predicting steroid-responsiveness as well as a mechanism through which steroids may exert an effect by altering IL-1β signaling pathways. However, the methodology incorporated in these studies has been questioned as their entry criteria and the audiometric criteria used do not conform to accepted norms.

Non-steroid Immunosuppressive Therapies for Autoimmune Inner Ear Disease

Given the undesirable side effects of long-term steroid treatment, significant proportion of patients with AIED who fail to respond to steroids, and frequent lack of sustained response to steroids over time, many have sought to identify alternative therapies (see Table 10.1 for summary). In McCabe's description of immune-mediated SNHL, he advocated the use of cyclophosphamide in addition to steroids (McCabe 1979). Other treatments described have included therapies such as plasmapharesis; immunosuppressive agents such as mycophenolate mofetil, methotrexate, and azathioprine; and biologic agents such as etanercept, adalimumab, infliximab, anakinra, and rituximab. Nonetheless, the relative rarity of AIED and often challenging diagnosis have resulted in a paucity of rigorous studies evaluating the efficacy of various treatment options relative to steroids. Indeed, a recent systematic review of non-steroid therapies for AIED concluded that "clear evidence of an effective treatment for AIED from high-quality prospective trials remains lacking" (Brant et al. 2015).

Table 10.1 Summary of immunosuppressive therapies investigated in AIED and their mechanisms

Therapy	Mechanism	Role in AIED
Corticosteroids (prednisone, prednisolone, dexamethasone, methylprednisolone)	Act on glucocorticoid receptor to influence transcription of a wide array of corticosteroid-responsive genes; results in up-regulation of anti-inflammatory cytokines and suppression of proinflammatory cytokines May also interact with mineralocorticoid receptor to control sodium reabsorption	Mainstay of treatment, showing benefit in both animal and human studies
Methotrexate	Inhibitor of dihydrofolate reductase, thereby interfering with DNA synthesis	Small retrospective and prospective series suggest benefit (Matteson et al. 2000; Sismanis et al. 2016; Lasak et al. 2001; Salley et al. 2001), however 1 RCT showed no effect compared to placebo (Harris et al. 2003)
Cyclophosphamide	Alkylating agent that cross-links DNA strands and disrupts cell growth and division; may act through other immunomodulatory mechanisms	Early case reports and small case series suggested benefit when used with steroids (McCabe 1979; Clements et al. 1989; Berrettini et al. 1998; Plester and Soliman 1989); equivocal results reported in retrospective studies (Broughton et al. 2004; Lasak et al. 2001; Veldman et al. 1993) Use limited by significant systemic toxicities
Azathioprine	Purine analog that interferes with nucleic acid metabolism	One uncontrolled prospective study suggested benefit when used with steroids (Saraçaydin et al. 2016); equivocal results in retrospective studies (Broughton et al. 2004; Lasak et al. 2001) Use limited by significant systemic toxicities

(continued)

Table 10.1 (continued)

Therapy	Mechanism	Role in AIED
TNF-α inhibitors (etanercept, infliximab, adalimumab, and golimumab)	Antagonists to the activity of TNF-α, a proinflammatory cytokine	Etanercept showed benefit in 1 uncontrolled prospective study (Rahman et al. 2001) while another was less favorable (Matteson et al. 2005); one RCT showed no benefit compared to placebo (Cohen et al. 2005) Infliximab improved hearing in case reports after failure of conventional therapies (Heywood et al. 2013; André et al. 2015); showed no benefit in 1 retrospective study (Liu et al. 2011); 1 small uncontrolled prospective study showed benefit of local infliximab infusion in patients who relapsed or could not wean from steroids (Van Wijk et al. 2006) IT gomalimumab did not clearly show benefit in a small prospective study (Derebery et al. 2014)
Anakinra	Competitive inhibitor of the IL-1 receptor type, part of IL-1 proinflammatory signaling pathway	Showed benefit in steroid non-responders in a small open-label, uncontrolled prospective study (Vambutas et al. 2014)
Rituximab	Monoclonal antibody against the CD20 antigen found on the surface of lymphocytes that results in elimination of B cells	Showed hearing benefit in a case report in a patient with Cogan's syndrome (Orsoni et al. 2010); no clear benefit in a retrospective study (Matsuoka and Harris 2013) 1 prospective study suggested patients able to maintain hearing gains from steroids with rituximab (Cohen et al. 2011)
Plasmapharesis	May remove autoantibodies, immune complexes, and other disease mediators from systemic circulation	Case reports show benefit in systemic autoimmune disease (Alpa et al. 2011; Hamblin et al. 1982; Kobayashi et al. 1992; Brookes and Newland 1986); one small prospective series did not show statistically significant hearing improvement with treatment (Luetje and Berliner 1997)

Abbreviations: *TNF-α* tumor necrosis factor-α, *IL-1* interleukin-1, *IT* intratympanic, *RCT* randomized controlled trial

Methotrexate

Methotrexate, an inhibitor of dihydrofolate reductase that is commonly used in the treatment of rheumatoid arthritis and other autoimmune and neoplastic disorders, is among the most studied alternative therapies to steroids for the treatment of AIED. In 1994, Sismanis et al. suggested methotrexate may hold benefit when they reported on a series of five patients with AIED who were treated with methotrexate, most of whom had discontinued steroid therapy due to adverse effects (Sismanis et al. 2016). Patients were given oral methotrexate 7.5 mg weekly, which was then increased to 15 mg weekly in most cases. The authors observed a significant improvement in speech discrimination after treatment as well as patient-reported symptoms of tinnitus and vertigo, though no significant change in PTAs. One patient experienced mild hair thinning, however methotrexate was otherwise tolerated well. Since then, other retrospective studies have indicated possible therapeutic benefit of methotrexate in stabilizing or improving auditory or vestibular symptoms associated with AIED, including one study that examined patients with bilateral Meniere's disease (Lasak et al. 2001). In particular, because methotrexate is well-tolerated over the long term, it was felt to be a promising substitute for prednisone in those patients whose disease was steroid-dependent.

Nonetheless, evidence from prospective studies is mixed. Several open-label, prospective studies of patients with AIED (two of which included patients with Meniere's disease and Cogan's syndrome) found hearing improved with methotrexate treatment in 53–82% of patients who had initially been treated with steroids (Matteson et al. 2000; Salley et al. 2001). However, the only randomized, placebo-controlled, double-blind trial aimed at assessing the efficacy of methotrexate in maintaining hearing improvements in patients with AIED after prednisone treatment did not show any benefit (Harris et al. 2003). One hundred and sixteen patients with AIED underwent a 1-month prednisone challenge and those patients deemed steroid-responders were then randomized to receive either methotrexate or placebo while being tapered from prednisone. Serial audiograms were obtained at defined time points during the study. The authors found no statistically significant difference in the rates of continued hearing loss in the methotrexate group compared to those in the placebo group, and concluded that methotrexate was no more effective than placebo in maintaining hearing improvement in patients with AIED who showed initial response to prednisone.

TNF-α Antagonists

Tumor necrosis factor-α (TNF-α), a cytokine that drives inflammation in many immune-mediated diseases, has been studied as a target for therapies treating AIED (Keithley et al. 2008). TNF-α has many actions in the inflammatory cascade, including attracting leukocytes to tissues and inducing apoptosis via the TNF receptor 1.

Moreover, it can induce recruitment of inflammatory cells from the systemic circulation into the cochlea (Keithley et al. 2008). Inflammatory cells infiltrating the inner ear expressed TNF-α and, to a lesser degree, IL-1β, in an animal model of immune-mediated labyrinthitis induced by systemic exposure to keyhole limpet hemocyanin (KLH) followed by injection of KLH into the cochlea (Satoh et al. 2002). Etanercept, a TNF receptor blocker, reduces hearing loss and the degree of inner ear inflammation in the KLH guinea pig labyrinthitis model when given systemically or when infused into the cochlea (Wang et al. 2003). Several biologic agents have been developed that act as antagonists to TNF-α activity and which are used in the treatment of various autoimmune conditions, including etanercept, infliximab, adalimumab, certolizumab, and golimumab.

Lobo et al. found etanercept to be as effective as corticosteroids in reducing hearing loss in the KLH guinea pig model, though human studies have shown mixed results (Lobo et al. 2006). A pilot study in human subjects with AIED who either failed or were intolerant of conventional therapies showed audiologic improvement in 7 of 12 subjects (58%) and stabilization in 4 of 12 subjects (33%) treated with subcutaneous injections of etanercept (Rahman et al. 2001). However, a subsequent open-label, prospective study of etanercept in 23 patients with AIED showed less favorable results, with improvement in only 30% of patients and stabilization in 57% of patients after 24 weeks of treatment (Matteson et al. 2005). Of note, both of these studies also included patients considered to have bilateral Meniere's disease. Cohen et al. conducted a blinded, randomized, placebo-controlled trial of 8 weeks of treatment with etanercept in 20 AIED patients and concluded that etanercept was no more effective than placebo in improving PTA or speech discrimination in this population (Cohen et al. 2005).

Infliximab, a monoclonal antibody that binds and inhibits TNF-α has also been investigated. A retrospective study of 8 patients with AIED refractory to steroids and cytotoxic therapy did not show any benefit of infliximab treatment in producing audiometric improvement, though one patient reported a subjective improvement in hearing (Liu et al. 2011). Case reports have described hearing improvement after infliximab treatment in a patient diagnosed with AIED who initially responded to steroids and azathioprine but continued to experience fluctuations and progressive decline in hearing, and in a congenitally blind woman with steroid-dependent episodes of SNHL and vertigo who was able to wean from steroids after starting infliximab (Heywood et al. 2013; André et al. 2015). Van Wijk et al. treated 9 AIED patients who relapsed from or could not be weaned from steroids with weekly infusions of infliximab delivered locally to the round window niche over a 4 week period (Van Wijk et al. 2006). The authors reported favorable results, with 4 of 5 patients who were steroid-dependent ultimately able to taper from steroids and 3 of 4 patients who had relapsed after the discontinuation of steroids showing improvements in their PTA.

In one case report, a patient with rheumatoid arthritis and SNHL recovered hearing after starting adalimumab, for treatment of her systemic autoimmune disease (Vergles et al. 2010). Intratympanic gomalimumab was studied as a treatment option in 10 patients with steroid-dependent AIED (Derebery et al. 2014). Gomalimumab

was injected into the tympanic membrane of a single ear over a 6-week period. At the study end, 6 of 10 subjects experienced stable PTAs in the injected ear while the remainder showed progression. Word recognition improved in 3 patients, worsened in 3 and improved in 4 injected ears. However, the non-injected ears also showed stable thresholds in 7 patients and stable word recognition in 7 patients. Seven of the ten patients enrolled were able to taper from steroids with 3 of those patients maintaining stable hearing overall.

Anti-TNF-α agents were generally well-tolerated in each of these studies, with no adverse effects reports with the exception of minor injection-site reactions in the case of etanercept (Rahman et al. 2001). The safety profile of these therapies in other autoimmune diseases has been generally been very favorable, though rare adverse effects that have been reported include lymphoma, tuberculosis reactivation, congestive heart failure, a lupus-like syndrome, infections, and skin eruptions (Scheinfeld 2009).

Anakinra

Anakinra, a competitive inhibitor of the IL-1 receptor type, has been investigated as a potential therapeutic option in select patients who fail steroid treatment given preliminary data reviewed above suggesting a role for IL-1β signaling in the pathogenesis of AIED (Vambutas et al. 2014). Case reports have linked anakinra to improved hearing in patients with Muckle-Wells syndrome, a hereditary autoinflammatory disorder characterized by urticaria, rash, fever, and progressive SNHL and whose pathogenesis is felt to involve IL-1β dysregulation (Mirault et al. 2006; Yamazaki et al. 2008). Vambutas et al. conducted a phase I/II, open-label, prospective trial of subcutaneous injections of anakinra in 13 subjects with AIED whose hearing failed to respond to corticosteroid treatment (Vambutas et al. 2014). Seven of the ten subjects who completed the treatment protocol showed improvement on audiometric assessment as well as a reduction in IL-1β plasma levels. The most common adverse event was an injection site reaction, which occurred in 70% of patients and led 2 subjects to drop out of the study.

The incorporation of anakinra into the therapeutic armamentarium for AIED would be attractive both because of its excellent tolerance and because it could also address possible ‘autoinflammatory’ etiologies. However, the currently available studies pertaining to the use of anakinra in this patient population have questionable validity. It is not clear that the patients included in these studies were steroid resistant or simply patients whose hearing initially fluctuated spontaneously, with some of these fluctuations occurring at the same time as the administration of steroids. Furthermore, the audiometric criteria used to define a positive therapeutic response do not meet currently accepted standards.

Azathioprine

Azathioprine, an immunosuppressive agent that interferes with nucleic acid metabolism and affects the rapidly dividing cells of the immune system, has been investigated as a potential therapeutic agent for patients with AIED in several small studies. Case reports have described improvement in SNHL linked with systemic autoimmune disease after treatment with azathioprine (Dowd and Rees 1987; Khalidi and Rebello 2008). One prospective, open-label study investigated the effects of azathioprine in addition to prednisolone on hearing outcomes in 12 patients with AIED (Saraçaydin et al. 2016). Ten of the twelve patients experienced significantly improved PTAs and speech discrimination after 4 weeks of treatment; the other two patients experienced no change in their hearing. No adverse events were observed related to azathioprine use. The authors did not test the effects of azathioprine alone or report long-term outcomes, so it is unclear if these results are due to azathioprine rather than the steroids, or if the hearing improvements observed are sustained.

One retrospective study of patients with AIED treated with steroids alone or steroids with a cytotoxic medication suggested that azathioprine may be beneficial in some of these patients (Lasak et al. 2001). Seven of the thirty-nine patients in the study were treated with azathioprine as a second- or third-line cytotoxic agent and after failing steroid therapy. Five of seven patients experienced audiometric improvement after a mean treatment period of 7 months. However, significant toxicities were observed: one patient experienced lymphoblastic vasculitis and another was diagnosed with pancytopenia/sepsis. Another retrospective study by Broughton et al. failed to demonstrate benefit of azathioprine treatment. The authors reviewed a series of 42 patients with AIED treated at their institution, of whom five received azathioprine at some point during their treatment (Broughton et al. 2004). One patient was treated for 30 months with stabilization of hearing. Three improved with azathioprine and steroids but experienced a relapse after tapering of steroids. One patient experienced subjective improvement in hearing and vertigo however discontinued the medication due to gastrointestinal upset. Given the small numbers of patients treated with azathioprine, lack of standardized treatment protocols, and retrospective nature of these studies, it is difficult to draw any conclusions about which, if any, patients with AIED may benefit from this treatment.

Cyclophosphamide

Cyclophosphamide is an alkylating agent used in various neoplastic and inflammatory diseases which acts by cross-linking DNA strands and disrupting cell growth and division in rapidly proliferating cells (Langford 1997). Though its use was described in the treatment of AIED in McCabe's first characterization of the disease, no rigorous, prospective studies have demonstrated its efficacy (McCabe 1979). Case reports and small case series have shown improvement in SNHL linked to

systemic vasculitis and Cogan's syndrome with cyclophosphamide, generally in conjunction with steroids (Clements et al. 1989; Berrettini et al. 1998; Plester and Soliman 1989). Veldman et al. found treatment with prednisone plus cyclophosphamide was no more effective in treating hearing loss than prednisone alone in a small series of patients with rapidly progressing SNHL (Veldman et al. 1993). In the retrospective review of 42 patients with AIED by Broughton et al., 6 patients received cyclophosphamide treatment (Broughton et al. 2004). Two of the six patients derived benefit, with hearing improving in one and stabilizing in another; 2 patients experienced continued hearing decline and 2 discontinued the medication due to adverse effects. In another retrospective review, 10 patients with AIED were given cyclophosphamide either as a first-line cytotoxic therapy after steroid failure or as a second-line therapy after methotrexate (Lasak et al. 2001). The authors reported a positive response in half of the patients over a mean treatment duration of 2.7 months.

Adverse effects related to cyclophosphamide use are frequent and severe. These include nausea and vomiting, serious infections, bone marrow suppression, hemorrhagic cystitis, infertility, teratogenicity, alopecia, pulmonary toxicity, and the malignancies including transitional cell carcinoma (Langford 1997). Thus, caution should be exerted with regard to its use in AIED given limited data showing efficacy.

Rituximab

Rituximab, a monoclonal antibody against the CD20 antigen found on the surface of lymphocytes, causes the elimination of B cells and is used in conditions felt to involve autoantibody production. Its use was reported to improve hearing in a woman with Cogan's syndrome with persistent hearing loss despite therapy with prednisone, cyclophosphamide, methotrexate, cyclosporine, and adalimumab (Orsoni et al. 2010). Matsuoka and Harris retrospectively reviewed treatment outcomes of 47 patients with AIED (including those considered to have immune-mediated Meniere's disease), of whom 5 had been treated with rituximab after failing steroids (Matsuoka and Harris 2013). Hearing improved in 2 patients, while all 5 experienced improvement in tinnitus, aural fullness, and vestibular symptoms and all reduced their dose of prednisone maintenance steroid. An open-label, pilot study of steroid-responsive AIED patients reported that 5 of 7 enrolled subjects were able to maintain the hearing improvement seen after steroids with rituximab infusions (Cohen et al. 2011). This effect persisted through 24 weeks of follow up, after steroids had been tapered off. No adverse events were reported.

Plasmapheresis

An alternative approach to the treatment of AIED that has been investigated is plasmapheresis, which may remove autoantibodies, immune complexes and other disease mediators from circulation. Luetje reported on eight patients with suspected

AIED, of whom four had been diagnosed with systemic autoimmune disease and who were treated with plasmapheresis (Luetje 1989). The patients in this small series had variable clinical courses with differing courses of treatment, including various combinations of steroids and cytotoxic medications. In some cases, plasmapheresis was used as an adjunct to steroids and/or cytotoxic medications, while in others, it was used as an alternative treatment while attempting to taper steroids. Thus, it is difficult to draw conclusions about the effect of plasmapheresis in each case. Overall, hearing was improved in 3 patients, declined in 2, and was essentially stable in the remaining 3 (though many patients experienced fluctuations throughout their clinical course). A follow up study, which included an additional 13 patients, reported longer-term results of plasmapheresis therapy (Luetje and Berliner 1997). Data was able to be collected on 28 ears from 16 patients who had at least 2 years of follow up (mean follow-up time: 6.7 years). Of those ears, 39.3% demonstrated audiometric improvement or stability during the follow-up period, though mean changes in speech reception thresholds and speech discrimination scores were not statistically significant. Only 4 of the 16 patients were using immunosuppressive medications at follow up. Other case reports have observed improvement after plasma exchange in a patient with sudden SNHL suspected to be of autoimmune origin, in patients with systemic lupus erythematous, and patients with SNHL associated with elevated serum immune complexes (Alpa et al. 2011; Hamblin et al. 1982; Kobayashi et al. 1992; Brookes and Newland 1986).

Additional Therapies

In the retrospective review by Broughton et al., intravenous gamma globulin was administered to one patient with AIED after failing treatment with methotrexate and discontinuing cyclophosphamide due to adverse effects (Broughton et al. 2004). The patient's hearing initially stabilized, but subsequently began to decline. However, the patient was able to taper to a lower dose of steroids and subjectively reported less severe fluctuations in hearing.

Mycophenolate mofetil, an immunosuppressive medication commonly used in solid organ transplantation, was successfully used to treat SNHL in a pediatric case of Cogan's syndrome, allowing the patient to taper off of steroids (Hautefort et al. 2009). Broughton et al. also report on one patient with AIED who failed azathioprine and methotrexate therapy and was treated with mycophenolate mofetil with good results (Broughton et al. 2004). The patient's hearing stabilized and steroids were able to be tapered to a low dose.

Cyclosporine, an immunosuppressive agent used in organ and bone marrow transplantation, was reported beneficial in a patient with steroid-dependent sudden SNHL, a patient with presumed AIED, and in a series of patients with SNHL associated with Behçet's disease (Elidan et al. 1991; McClelland et al. 2009; Di Leo et al. 2011). However, of note, this drug has also been associated with the development of hearing impairment in transplant patients (Gulleroglu et al. 2015; Rifai et al. 2005; Marioni et al. 2004).

3 Idiopathic Sudden Sensorineural Hearing Loss

Corticosteroids have long been the mainstay of treatment for idiopathic sudden sensorineural hearing loss (ISSHL), initially given empirically in early reports under the hypothesis that their anti-inflammatory effects could be beneficial in presumed cases of virally-mediated hearing loss (Glasscock et al. 1971; Whitaker 1980). The first systematic, prospective, placebo-controlled, double-blinded study of the use of steroids in patients with ISSHL appeared in 1980 when Wilson et al. showed recovery of hearing in patients with moderate hearing loss after treatment with steroids (Wilson et al. 1980). Since then, an abundance of retrospective studies have appeared which purport to show beneficial effects of systemic steroids in this population (Byl 1977; Moskowitz et al. 1984; Fetterman et al. 1996; Zadeh et al. 2003; Slattery et al. 2005; Chen et al. 2003). However, a Cochrane review first published in 2006 and updated in 2013 found only 3 randomized controlled trials evaluating the used of steroids in ISSHL that met the authors' inclusion criteria, including the study by Wilson et al. (2006). Among the two other studies included in the review, neither showed a statistically-significant difference in hearing recovery in steroid-treated patients versus controls. Due to the small size of the included studies, inconsistent treatment protocols, differing definitions of hearing recovery, and methodological limitations of the included studies, the review authors write that "no conclusions can be drawn about the effectiveness, or lack thereof, of steroids in the treatment of idiopathic sudden sensorineural hearing loss." Two recent meta-analyses support this finding in its failure to find a statistically-significant treatment effect of steroids over placebo (Crane et al. 2015; Conlin and Parnes 2007).

Despite limited data to support the use of steroids in prospective studies, current clinical practice guidelines recommend offering a short course of steroids in patients without contraindications as steroids are one of the few treatment options with any evidence to support its use (though it may only be retrospective in nature); moreover, the risk of serious adverse effects in short-term use of steroids is low while the consequences of a major hearing loss can be quite significant (Stachler et al. 2012). These guidelines suggest the use of oral prednisone 1 mg/kg/day (up to a maximum of 60 mg daily) for 10–14 days, with therapy being initiated within the first 2 weeks of symptom onset as recovery is greatest during this time window.

Intratympanic steroids represent a promising alternative to systemic steroids and have been extensively studied recently both as a primary treatment for ISSHL or as salvage therapy after failure of systemic steroids. A multi-center, randomized trial demonstrated that IT methylprednisolone was not inferior to oral prednisone in the treatment of ISSHL (Rauch et al. 2011). A meta-analysis examined 8 randomized controlled trials evaluating the efficacy of IT dexamethasone in treating ISSHL (Sabbagh El et al. 2016). The studies differed in the dosing regimen, technique of drug administration, and whether or not dexamethasone was the first- or second-line therapy. Hearing improvement was reported in 50–80% of subjects in the IT dexamethasone arms, though the meta-analysis did not find a statistically-significant difference between the steroid and control groups. However, two studies did show a

significant improvement in hearing in the treatment arm compared to controls, both of which used IT dexamethasone as a salvage therapy after failure of conventional treatment and both of which used a drug concentration of 4 mg/mL (Wu et al. 2011). Crane et al. examined randomized controlled trials involving any IT steroid, specifically the subset in which IT steroids were used as salvage therapy (Crane et al. 2015). In a meta-analysis of these studies, the authors did find a significant treatment effect of IT steroids with an odds ratio of 6.04, though they caution that poor quality of the studies comprising the analysis limit interpretation of these results. As IT steroids have been found beneficial, current practice guidelines recommend offering this therapy in patients with ISSHL who fail systemic steroids. In patients with diabetes, IT steroids may be attractive as an initial treatment option in order to avoid uncontrolled hyperglycemia (Han et al. 2009). Finally, side effects of IT steroids tend to be minor, and have included otalgia, aural fullness, headache, temporary dizziness/vertigo, and tympanic membrane perforation (Sabbagh El et al. 2016).

Steroids remain the only anti-inflammatory therapy whose use in ISSHL has been extensively investigated. Clarifying the role of these therapies in ISSHL remains challenging since, by definition, the pathogenesis of ISSHL is unknown and has been proposed to involve as varied mechanisms as viral infection, vascular occlusion, immune dysfunction, and membrane breaks within the inner ear. More recently, ISSHL was hypothesized to involve the abnormal activation of cellular stress pathways (Merchant et al. 2005). Likely, multiple etiologies may combine to result in a similar clinical presentation. If different pathogenic events are found to be mediated through common inflammatory or immunologic mechanisms, a new role for anti-inflammatory treatments may emerge. For example, a study in guinea pigs suggested that inhibitors of TNF signaling could reverse TNF-induced reductions in cochlear blood flow, suggesting a pathway through which modulation of inflammatory pathways could affect the microvascular disturbances which have been postulated to cause a subset of ISSHL (Sharaf et al. 2016). Further research into the complex interactions between inflammatory events and cochlear injury will lead to the identification of targets for future therapies. Many alternative, non-immunomodulating therapies have also been studied for use in ISSHL including antivirals, vasodilators, antioxidants, vitamins, fibrinogen or LDL apheresis, and hyperbaric oxygen; none of these interventions, however, with the exception of hyperbaric oxygen, are supported by enough evidence to merit recommendation in clinical practice guidelines (Conlin and Parnes 2007; Stachler et al. 2012; Suckfüll 2002; Agarwal and Pothier 2009; Angeli et al. 2012; Sano et al. 2010; Hatano et al. 2009; Westerlaken et al. 2016).

4 Conclusion

Anti-inflammatory therapies have played an important role in the treatment of AIED and ISSHL. Corticosteroids are the most commonly employed immunosuppressive medication in these disorders, though the exact mechanisms through which they act

in the inner ear is unknown. Intratympanic steroids may also benefit patients with ISSHL who fail systemic steroid therapy, or may be a preferable first-line treatment in patients with diabetes. A variety of immunosuppressive therapies have been studied in the treatment of AIED on the basis of their effectiveness in other autoimmune and inflammatory conditions. These have included cyclophosphamide, methotrexate, azathioprine, rituximab, anakinra, anti- TNF-α agents, and plasmapharesis. While studies of these agents have suggested improvement or stabilization of hearing loss in some cases, these studies are generally limited by small sample sizes and are often retrospective or observational in nature, and lack adequate controls. Furthermore, they may have significant side effects, the risks of which may not be acceptable in an era in which cochlear implantation is a viable option. Further elucidation of potential immunologic or inflammatory mechanisms underlying different forms of SNHL may pave the way for the development of targeted therapies for inner ear disorders.

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