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Emerging Options in Immune-Mediated Hearing Loss

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Objective: AIED (autoimmune inner ear disease) is an autoimmune process that leads to the dysfunction of the inner ear, resulting in fluctuating, audiovestibular symptoms. Although the pathogenesis is likely heterogeneous, immune processes within the inner ear ultimately lead to histopathologic changes and sensorineural hearing loss. This review will discuss the latest evidence on treatment options.

Methods: A literature search on articles pertaining to the treatment of autoimmune inner ear disease was performed on PubMed.

Results: Corticosteroid treatment continues to remain as first line therapy for AIED but long-term responsiveness is poor. Cytotoxic chemotherapies can be effective alternatives for steroid nonresponsive patients, but significant side effects may limit their use. Intratympanic steroid injections are beneficial and although there is not enough evidence currently to supplant oral steroid trial they may be a useful adjunct if steroid toxicity is an issue. The efficacy of biologic agents has been variable. Compared to placebo, etanercept does not improve the hearing improvement already attained by steroids alone. However, open pilot studies of other biologic agents show hearing improvements, improvements in tinnitus/aural fullness/vertigo, ability to wean steroid dependency, or benefits in steroid-resistant AIED.

Conclusion: There is currently not enough evidence that alternative treatments supersede the use of initial steroid treatment. Biologic agents and intratympanic steroid injections are relatively well tolerated and should be considered as adjunctive therapy. More studies on the efficacy of various biologics and more studies on the treatment of steroid resistant disease especially after initial benefit are still needed. For those who eventually lose their hearing, cochlear implantation remains as a viable option.

Key Words: Autoimmune inner ear disease, AIED, Cogan's syndrome, immune mediated hearing loss, biologics.

Level of Evidence: expert opinion.

INTRODUCTION

Autoimmune inner ear disease (AIED) typically presents with bilateral, fluctuating audiovestibular symptoms, and can be associated with a variety of autoimmune disorders. These include, but are not limited to, Vogt-Koyanagi-Harada syndrome, Cogan's syndrome, Susac's syndrome, systemic lupus erythematous, rheumatoid arthritis, granulomatosis with polyangiitis (ie, Wegener's granulomatosis), Behçet's disease, systemic sclerosis, inflammatory bowel disease (eg, Crohn's, ulcerative colitis), relapsing polychondritis, and temporal arteritis. AIED can also be suspected in patients without systemic symptoms, based on laboratory markers of autoimmune or autoinflammatory processes (eg, OTOblot, Buffalo, NY, USA; erythrocyte sedimentation rate; C-reactive protein; rheumatoid factor; anti-nuclear antibody; anti-double-stranded DNA; cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA); and Complement C3, C4, and C1q) after ruling out infectious causes such as syphilis and human immunodeficiency virus (HIV). These tests can also aid in the classification of AIED.[1]

Cogan's syndrome was one of the earliest defined syndromes of hearing loss described in the 1950s. He characterized several case series[2–4] of nonsyphilitic progressive bilateral vestibuloauditory disorders associated with keratitis and other systemic symptoms. McCabe,[5] however, was the first to link Cogan's syndrome with an autoimmune process and to recommend treatment with a combination of cyclophosphamide and dexamethasone. Since then, the responsiveness of the hearing loss to steroids has been an important indicator for diagnosing AIED; although, as we later discuss, not all AIED is steroid responsive.

The incidence of AIED is estimated to be less than 5 in 100,000[6] and represents less than 1% of all SNHL. Although it can be unilateral, it often affects both ears. Symptoms usually fluctuate over the course of weeks to months, distinguishing it from presbycusis which occurs over the course of years. The clinical presentation of AIED may overlap with that of Meniere's disease and can be difficult to distinguish from it. Thus, the presence of additional systemic autoimmune findings, diagnosis of autoimmune disorder, or laboratory findings of autoimmune markers may aid in the diagnosis.

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PATHOGENESIS

The inner ear is not an immunologically privileged site. Early electron microscopy studies by Rask-Anderson and Stahle suggest that the endolymphatic sac may be the site of immunological processing.[7] Subsequent studies by Mogi and by Harris have shown that peripheral immunization of animals can lead to antibody concentration within the inner ear.[8–10] The presence of the endolymphatic sac is necessary for the immune response.[11] The pathway of entry into the inner ear is suspected to be via the spiral modiolar vein[12,13] with entry of inflammatory cells into the scala tympani.[14] The cells are thought to then proliferate and release inflammatory mediators that initiate a cascade of events leading to hearing loss.[12,14–16]

It is not known what triggers the autoimmune response. There are some studies that suggest that autoantibodies are produced against inner ear protein through molecular mimicry in response to viral or bacterial infection. For example, viral infection has been proposed to lead to autoantibodies in Cogan's syndrome which recognize peptide sequences that are similar between REOVIRUS III core protein lambda and autoantigens DEP-1/CD148 (found on endothelium) and Connexin 26 (found in the inner ear).[17] T-cells may also be involved in AIED. T-cells recognizing cochlin, an abundant inner ear protein has been found frequently in AIED patients.[18]

It is known that one-third of patients with suspected AIED have circulating antibodies that recognize a 68kDa inner ear protein by Western blot.[19] Heat shock protein 70 (HSP70) has been proposed to be one protein that correspond to this molecular weight.[20] It is a ubiquitously expressed housekeeping protein and, therefore, immune response to this protein is thought to be a bystander effect, not an actual cause for hearing loss. The identification of the 70kDa protein band on Western blot of inner ear proteins using patient serum antibodies had been the basis for the OTOblot test. Unfortunately, the commercialized test now uses recombinant bovine HSP70, which is less sensitive than the original test using inner ear protein extract. A recent study comparing AIED patients to controls found that the rate of OTOblot positivity was no different.[21] These results suggest that the test in its current form is not useful. Sera from patients with progressive hearing loss also react to additional proteins from inner ear (eg, myelin protein P0, 27-30kDa, 33-35kDa, 45kDa, 50kDa, 58kDa, 80kDa).[22–25]

HISTOPATHOLOGY

There are a number of histopathologic changes that can occur in the inner ear as a result of AIED. Endolymphatic hydrops (excessive fluid expansion in the scala media) is a common finding in the temporal bones of AIED patients.[26] Consistent with this, abnormal ECoG (electrocochleography) test is observed in more than half of AIED patients.[27] Patients with Meniere's symptoms also have a higher rate of systemic autoimmune disease compared to what is expected in normal population.[28] In animal models, antigen challenge either in the inner ear or with inner ear antigens consistently results in endolymphatic hydrops.[29–31]

The autoimmune process can result in direct destruction of inner ear structures. In Wegener's granulomatosis, vasculitis is observed in the cochlea, vestibule, and facial nerve.[32] Basement membrane Immunoglobulin G deposition and loss of spiral ganglion neurons have been observed in Sjögren's.[33] Atrophy of the stria vascularis and loss of spiral ganglion cells are observed in systemic lupus erythematous.[34–36] These inflammatory processes result in fibrosis and osteoneogenesis[37–39] and retrograde neuronal degeneration.[26]

TREATMENT

The treatment of AIED mirrors the treatment for systemic autoimmune disease. Corticosteroids are the primary therapy, followed by chemotherapy for steroid nonresponders.[40,41] The results for biologics are promising, but heterogeneous, and there is still insufficient randomized control trial evidence for its use as a first-line therapy.[42] We discuss the current evidence for the various AIED treatments below.

Systemic Steroids

Not all the pathways by which glucocorticoids decrease inflammation are elucidated. It is known that glucocorticoid effects are mediated through transcriptional regulation.[43] A simplified model of how steroids decrease inflammation is schematically shown in Figure 1. In the "transactivation" model, glucocorticoids

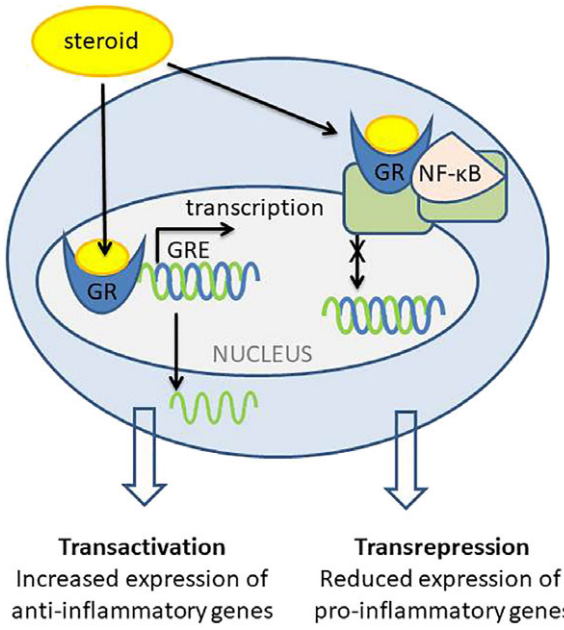

Figure 1. Mechanism of steroids.
Glucocorticoid steroid crosses cellular membranes and binds the GR (glucocorticoid receptor) which is a DNA binding protein. Together they translocate to the nucleus and activate the expression of anti-inflammatory genes that contain GRE (glucocorticoid response element) sequences. Glucocorticoids can also inhibit NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) transcription factor and indirectly inhibit the expression of pro-inflammatory genes such as cytokines.

diffuse through cells and bind glucocorticoid receptors, causing their translocation into the nucleus where they increase the expression of genes containing glucocorticoid response element (GRE) sequences. The result is an increase of anti-inflammatory gene expression. In the "transrepression" model, glucocorticoids inhibit transcription factors, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and indirectly suppress the expression of pro-inflammatory genes such as cytokines (eg, tumor necrosis factor α [TNFα]).

Steroids are very effective immunosuppressants and are effective in improving hearing loss in AIED but the effects are not long lasting. Initial response rate is 50% to 70%.[27,44–46] A typical regimen used by the senior author is prednisone at 60 mg/day or (1 mg/kg) for at least one month[47] or until symptoms stabilize, followed by a taper. Unfortunately, many people who benefit from steroids can develop resistance or relapse after taper, and only 14% remain steroid responsive by 34 months.[27] Tinnitus has been found to be a sensitive predictor of relapse.[46] If relapse occurs, steroids are resumed, however, prolonged systemic steroid use is not ideal due to side effects.

Common side effects of long-term steroid use include insulin resistance, obesity, osteoporosis, immunosuppression, gastric ulcers, adrenal suppression, and psychiatric disturbances.[47–49] When initiating short-term high-dose steroid treatment, it is important to consider preexisting conditions that may be worsened, including diabetes, high blood pressure, and psychiatric illness such as anxiety and depression, and discuss the risks and benefits of treatment with the patient. When continuing on long-term steroids, it is important to engage the patient's primary care physician for close monitoring of weight, complete blood count, glucose, lipid, and osteoporosis and cardiovascular risks,[49] and for vigilance related to the other potential adverse drug reactions discussed above.

Intratympanic Steroid Injection

In animal studies, higher level of steroids is measured in perilymph after intratympanic (IT) steroid injection compared to systemic administration.[50] In retrospective studies, IT steroid injection has been shown to improve hearing in 54% (6 of 11) of oral steroid refractory patients[51] and in 50% (15 of 30) of patients overall.[46] There is currently no randomized control trial examining the effect of IT versus oral steroids in AIED, thus, there is not enough evidence to recommend that IT steroids should be administered in lieu of oral route. However, it is a relatively safe adjunctive or second line therapy.

Chemotherapy

Cyclophosphamide is an effective cytotoxic alkylating agent and immunosuppressant (see Table I). McCabe used a combination of steroids and cyclophosphamide on all of his patients and had on average 15 dB pure tone improvement and 20% speech discrimination score improvement.[51] It cannot be determined how much the effect was attributed to cyclophosphamide versus steroids. Since then, there is very limited data aside from a few case reports. In a more recent retrospective study the results have not been as good: of 6 patients treated with cyclophosphamide, only 2 had improved or stable hearing, 2 had no response, and 2 dropped out due to side effects.[27] Significant side effects preclude its use, including myelosuppression, nausea, alopecia, infertility, increased risk for infection, and malignancy. Close monitoring with complete blood count, liver function test and urinalysis is needed.

Methotrexate is an immunosuppressant that is better tolerated than cyclophosphamide (see Table I for mechanism of action). The drop-out rate due to toxicity is less than 10%.[27,52,53] Toxicity includes myelosuppression, mucosal ulcerations, liver toxicity, renal failure, pneumonitis, teratogenicity, and increased lymphoma risk. With the exception of one retrospective study, which showed no hearing improvement in 83% despite treatment with methotrexate,[27] many open-label studies had shown promising results. The drug improved hearing in 50% to 70% of steroid responsive patients[52–55] and improved vestibular symptoms in 80% to 100%.[54,55] However, a randomized control trial of 67 steroid responsive AIED patients showed that the addition of methotrexate at the end of steroid taper was no more effective than placebo in maintaining the hearing improvement achieved by steroids.[48]

There are alternative drugs such as azathioprine[27,56,57] and mycophenolate,[58] but they are less well studied.

Plasmapharesis

Plasmapharesis is typically reserved in severe cases of autoimmune disorder that progress rapidly with vasculitis, leukopenia, thrombocytopenia or organ involvement despite immunosuppression.[59] It has been reported to help stabilize hearing when it has been used.[60,61]

TABLE I.
Anti-inflammatory Mechanisms of Methotrexate and Cyclophosphamide

Methotrexate
Inhibition of purine biosynthesis → elevated extracellular adenosine levels → downregulation of T-cells and inflammation *(this is thought to be the major pathway)*
Antagonism of folate → inhibition of DNA synthesis → apoptosis and T-cell reduction *(this is the main pathway for the chemotherapeutic effects but is not thought to be the major pathway for reducing inflammation)*
Cyclophosphamide
Metabolism by cytochrome-P450 into phosphoramide mustard → adds alkyl group to guanine base of DNA → inhibition of DNA replication → cell death, affecting both resting and dividing lymphocytes.

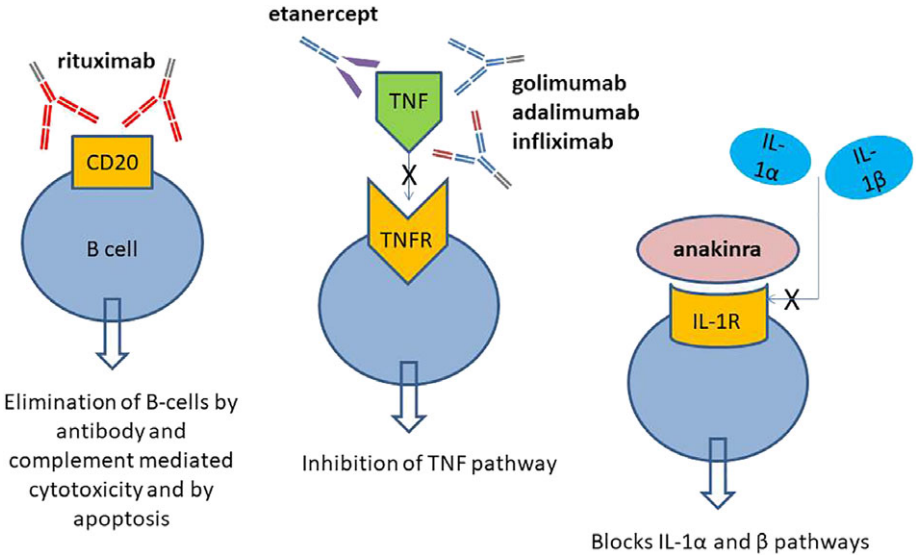

Figure 2. Mechanism of biologic agents.
Rituximab targets CD20 antigen on B-cell membranes, causing reduction of B-cells by apoptosis or by complement and antibody mediated cytotoxicity. Etanercept, golimumab, adalimumab and infliximab targets TNF (tumor necrosis factor) and prevents its effects through TNFR (TNF receptor). Anakinra is a IL-1R (IL-1 receptor) agonist and competitively reduces the activity of both IL-1α and IL-1β.

Biologic Agents

An exciting development in the last 10 to 15 years has been the introduction of biologic agents for the treatment of autoimmune disease. These are engineered antibodies that target specific molecules of the immune system. There are generally three types that are being investigated in AIED (see Fig. 2 and Table II). One group targets TNFα (eg, infliximab [Remicade], adalimumab [Humira], golimubab [Simponi], and etanercept [Enbrel]. Another targets B-cells (eg, rituximab [Rituxan]). And a third targets IL-1beta (eg, anakinra [Kineret]). These biologics can suppress the immune system and there is increased risk for upper respiratory infections, neutropenia, and infusion site reactions. However, a study reviewing clinical trials of various biologics found that, although newer TNFα inhibitors have higher side effect profile, overall, there was no significant difference in the risk of infection, infusion site reaction, malignancy, or mortality between control and experimental groups.[62] These drugs are relatively well tolerated.

TABLE II.
List of Biologics Used for AIED and Relevant Literature

Agent	Structure/Target	Reference	Study Details
TNFα inhibitor			
Infliximab (Remicade)	Human-mouse chimeric monoclonal antibody targets soluble and membrane TNFα	Van Wijk et al., 2006	Prospective pilot study on transtympanic infliximab, n = 9.
Golimumab (Simponi)	Human monoclonal antibody targets soluble and membrane TNFα	Derebery et al., 2014	Open label study on transtympanic golimumab, n = 7.
Adalimumab (Humira)	Human monoclonal antibody targets soluble and membrane TNFα	Matsuoka et Harris, 2013	Retrospective review, n = 10.
Etanercept (Enbrel)	TNF receptor fused to human antibody targets soluble and membrane TNFα	Rahman et al., 2001	Cites a meeting abstract reporting a pilot study, n = 12.
		Matteson et al., 2005	Open label pilot study, n = 23.
		Cohen et al., 2005	Pilot placebo-controlled trial, n = 10 each arm.
B-cell inhibitor			
Rituximab (Rituxan)	Human-mouse chimeric monoclonal antibody targeting CD20 on B-cell membranes	Cohen et al., 2011	Open label pilot study, n = 7.
		Matsuoka et Harris 2013	Retrospective review, n = 5.
IL-1 inhibitor			
Anakinra (Kineret)	Recombinant form of IL-I receptor antagonist (IL-1Ra) which blocks IL-1 receptor and reduces the activities of both IL-1α and IL-1β	Vambutas et al., 2014	Phase I/II open label, single-arm clinical trial, n = 10.

Note: Case reports not included. TNF (tumor necrosis factor); IL-1 (interleukin-1); CD20 (cluster differentiation 20).

TNFα Antagonists

TNFα is a pro-inflammatory cytokine and is an indicator of steroid responsiveness in AIED.[63] Using an established mouse model of AIED immunized with KLH antigen, etanercept has been found to decrease the number of infiltrating cells in the cochlea in response to TNFα.[64] Several open-pilot studies show variable hearing results with etanercept in steroid responsive patients. In one reported study of 12 patients, 58% had hearing improvement.[65] In another with 23 patients, 30% had improved hearing and 58% had stable hearing.[66] However, a pilot placebo-controlled study of steroid responsive AIED patients found no difference in the hearing improvement between etanercept and placebo.[67]

Yet another TNF αantagonist, infliximab, delivered by local intratympanic (IT) infusion once weekly for 4 weeks has been found to stabilize hearing and allow 4 of 5 steroid-dependent patients to wean off steroids, or improve hearing loss in 3 of 4 steroid-responsive patients who relapsed after steroid cessation.[68] Another study of 10 steroid-dependent AIED patients who underwent IT golimumab therapy found that 6 had stable thresholds in the injected ear and 7 patients were able to wean off steroids.[69]

TNFα antagonist is not useful in steroid refractory AIED. In a study of 8 patients who did not respond to steroids, systemic treatment with infliximab was not helpful in hearing improvement.[70]

IL-1β Antagonists

One of the challenges of AIED is the treatment of steroid nonresponders. While steroids are known to suppress IL-1β through indirect pathways, one study suggests that the IL-1β pathway is abnormally upregulated in steroid resistant patients.[71] They also showed that IL-1β antagonist anakinra can decrease IL-1β in otherwise steroid-nonresponsive monocytes. This is promising for the potential use of anakinra for steroid-nonresponsive patients. A phase I/II study showed that in an intention to treat analysis, 58% response rate with anakinra injection in steroid-nonresponsive AIED.[72] The drug was well tolerated, aside from a risk of injection site reaction rate of 70%.

B-Cell Antagonists

Rituximab is a B-cell inhibitor targeting CD20. A small open pilot study of 7 patients tolerated rituximab without significant side effects and 5 were able to maintain the post-steroid hearing improvement.[73] There is one case report of a Cogan's syndrome patient who did not respond to prednisone, methotrexate, cyclophosphamide, cyclosporine, and adalimumab (TNFα inhibitor), but did have hearing improvement after rituximab.[74] In a retrospective study, hearing improved in only 2 of 5 treated with rituximab, but all patients improved tinnitus, aural fullness, and vertigo.[46]

Cochlear Implantation

For those patients whose hearing could not be salvaged, cochlear implantation is an excellent rehabilitative option.[75–77] Although neo-ossification (which required drill out) and intraluminal fibrosis was seen in 50% of implanted ears, all ears were implanted and the outcomes on word and sentence scores were not significantly different between AIED and postlingually deaf control patients.[75] This option is especially important for those patients unable to tolerate the side effects of immunomodulating drugs and go on to develop bilateral deafness.

DISCUSSION

Assessment of AIED treatment is difficult because of the scarcity of patients to perform large clinical trials. Currently, there is no randomized control study comparing steroids to alternative medications. Therefore, at this time, the use of alternative drugs cannot be recommended as a substitute for initial steroid trial.

Currently, steroids are a consistently effective for AIED in more than half of patients. There are two problems. One is that the effects are not long lasting. In patients who relapse, the current recommendation is to resume steroids but this is not a great long-term solution given its side effects. Unfortunately, placebo controlled studies suggest that use of alternative medications such as methotrexate and etanercept do not improve upon the hearing results already attained by steroids.[48,67] These results could be explained because the effects of medications could have been dampened by the steroid effects. Also, different biologics may have variable effects. Open pilot study on rituximab suggests that it may help maintain hearing achieved by steroids.[73] Studies suggest that IT injection of infliximab and golimumab[68,69] can help patients wean off steroid dependency. In our experience (unpublished), we have found rituximab and adalimumab therapy can be helpful in weaning steroids either completely or to low tolerable doses of 10 mg/day. It is worth considering the use of biologics as a maintenance medication in an attempt to wean steroid dependence.

The second problem is the dilemma of treating patients who are refractory to steroids. Chemotherapy is the usual next step, however, significant side effects are the primary reason many patients and providers have shied away from cyclophosphamide. Methotrexate appears to be better tolerated. We do not know how effective they are in steroid nonresponders because many large-scale studies have selected for steroid-responsive patients. IT steroid injection has been shown to be helpful in half of steroid nonresponders[55] and should be recommended. Can we also consider biologics? Studies suggest that the TNFα antagonists likely affect steroid pathways, and may explain why these drugs are not helpful in steroid nonresponders.[70] There are some suggestions that other cellular pathways, such as IL-1β, may be abnormally regulated in steroid nonresponders and can serve as alternative therapeutic targets.[71] IL-1β phase I/II study showed promising results using anakinra biologic,[72] but more studies are needed before strong recommendations can be made.

Although the benefits of chemotherapy and biologics on hearing improvement have been variable, what is underappreciated is the apparent benefit of biologics on other aural symptoms of fullness, vertigo, and tinnitus. In a retrospective study, less than half of patients treated with adalimumab or rituximab had hearing improvement but >80% had improved tinnitus, aural fullness, and vertigo.[46] Similarly with methotrexate, the improvement rate for vestibular symptoms can range from 80% to 100%.[54,55] Thus, one should not eliminate the use of nonsteroid treatment based on lack of hearing improvement alone.

CONCLUSION

Whatever the initial insult or trigger may be, the autoimmune process leads to destructive changes in the inner ear and ultimately neural degeneration and hearing loss. Thus, the most effective treatments have been focused on modulating the immune system. Corticosteroids continue to remain the most effective and primary recommended treatment. Currently, there is not enough evidence to recommend the use of alternative medication to replace an initial steroid trial. Intratympanic steroid injection and chemotherapies remain as alternative options that can be considered, especially in steroid nonresponders, but with the latter pose significant side effects that may limit their use. Promising advancements have been made in biologics in the treatment of autoimmune disorders. The effects on hearing improvement have been variable with various biologics, suggesting that the effect of one biologic is not generalizable to others. Aside from the effects on hearing, there is evidence of the usefulness of biologics in weaning steroid dependency, treatment of steroid nonresponders, and the potential benefits in vertigo, aural fullness, and tinnitus. More studies are needed on the effectiveness of each biologic and more studies are needed on the treatment of steroid nonresponsive patients. Ultimately, if hearing is lost, cochlear implantation is a very effective treatment option for these patients.

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