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Intratympanic Dexamethasone in the Treatment of Ménière's Disease: A Comparison of Two Techniques

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Objective: To assess the efficacy and safety of two different intratympanic dexamethasone (IT Dex) injection protocols for intractable unilateral Ménière's disease.
Study Design: Prospective case series.
Setting: Tertiary neurotology clinic.
Patients: One hundred six consecutive adult patients with definite unilateral Ménière's disease who had failed medical management were studied for an average of 1,061 days. None had previous oral steroid, IT steroid, or ablative treatment.
Interventions: Two different IT Dex regimes, either a single injection or a series of four injections, that were subsequently repeated as indicated.
Main Outcome Measure: Requirement for subsequent ablative therapy in the form of intratympanic gentamicin, vestibular nerve section, or labyrinthectomy. Hearing outcomes were measured using pure-tone average of 0.5, 1, 2, and 3 kHz on standard audiometry.
Results: The number of intratympanic dexamethasone injections per patient ranged from 1 to 29 (median = 4). Using the Kaplan–Meier method, predicted survival (patients not requiring ablative therapy) at 2 and 4 years after initial treatment was 83.9 and 79.3%, respectively. The injection series protocol ultimately yielded 5% better survival than the single injection protocol, but this was not statistically significant. Injections did not protect against hearing loss, and the most recent pure-tone averages declined compared with pretreatment values by an average of 8.27 dB ($p < 0.05$). The treatments did not result in any acute hearing losses, permanent tympanic membrane perforations, or other significant adverse events.
Conclusion: Intratympanic dexamethasone injections were successful in controlling vertigo insofar as they were able to obviate ablative therapy in the majority of Ménière's disease patients in this study. The injection series protocol may have been more beneficial compared with the single injection, although the difference between the two protocols was nonsignificant. Hearing mildly declined over the treatment course, which likely represents natural disease progression. The lack of adverse events suggests that IT Dex may be a nonablative option for patients with bilateral disease or only hearing/vestibular ears. **Key Words:** Dexamethasone—Hearing loss—Intratympanic injection—Ménière's disease—Steroids—Vertigo.

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Since Prosper Ménière's characterization in 1861 of the disease that now bears his name, the exact pathophysiology of this disease has remained elusive (1). Symptoms include vertigo episodes lasting 20 minutes or more, tinnitus, aural fullness, and fluctuating sensorineural hearing loss (2). The commonly held theory is one of endolymphatic hydrops, due to a disruption of the normal balance between endolymph production and absorption. Many of the medical treatments are directed toward this overabundance of endolymph. First-line management includes dietary salt restriction, diuretics, and betahistine (3). The neurotology clinic at the London Health Sciences Centre began offering intratympanic dexamethasone treatments (IT Dex) in 2009 for those patients who failed maximal medical therapy. Treatment failures of IT Dex were offered ablative therapy in the form of intratympanic gentamicin (IT Gent), vestibular nerve section, or labyrinthectomy depending on the disease progression and the level of hearing. The senior authors do not perform endolymphatic sac surgery for Ménière's disease on the basis that the risks have been shown to outweigh the potential benefits (4).

The use of intratympanic corticosteroid injection has become increasingly common in the management algorithms of Ménière's disease (5). Compared with systemic administration of steroids, intratympanic injection achieves higher inner ear drug concentrations, and the avoidance of systemic side effects (6). Entry is gained to the inner ear perilymph via passive diffusion through the

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round window, the oval window annulus, as well as the bony otic capsule (7). The presumed mechanisms of action of corticosteroids in the inner ear are anti-inflammatory and fluid/ion homeostasis (3). While many patients report subjective improvement in the severity and frequency of their vertigo spells, there is conflicting evidence of this modality's treatment success in the literature. Furthermore, dosing concentration and frequency vary widely between studies (5). Phillips and Westerberg (8) performed a Cochrane review of intratympanic steroids for Ménière's disease and only one randomized placebo-controlled study by Garduño-Anaya et al. (9) met their selection criteria. In this study, patients were treated with five consecutive daily injections of intratympanic dexamethasone (4 mg/ml) or placebo, vertigo control at the 2-years follow-up was class A in 82% of dexamethasone-treated patients and only 57% of placebo patients (9). Phillips and Westerberg (8) concluded that the results of a single trial only provide limited evidence to support intratympanic steroid effectiveness. A recent randomized double-blind placebo-controlled study of a sustained release intratympanic dexamethasone injection demonstrated a trend toward better vertigo control at higher steroid doses, measured at 3 months postinjection (10). Furthermore, a 2008 report by Boleas-Aguirre et al. (11) used a survival analysis in which vertigo was considered to be controlled after IT Dex when ablative therapy in the form of IT Gent was not needed. They had a 91% ''survival'' rate at 2 years after the initiation of treatment. Treatments were given on an ad hoc basis, and the number and frequency of treatments varied considerably from patient to patient.

As such, London Health Sciences Centre began to routinely offer IT Dex to patients after the Boleas–Aguirre report in 2008, and data were collected prospectively to assess the success of this modality. This study was designed to evaluate patients treated with two different regimens of IT Dex and to document those who failed treatment and required ablative therapy. Audiometric data and adverse events were collected throughout treatment as per the study protocol.

METHODS

Ethical Considerations

This study was approved by the University of Western Ontario Health Sciences Research Ethics Board (Protocol #16930E).

Participants

Patient data was collected at the London Health Sciences Centre adult neurotology clinic from 2008 to 2015. All patients with active definite unilateral Ménière's disease according to the 1995 AAO-HNS criteria (12) were initially treated with maximal medical therapy, which included lifestyle modifications, a low-salt diet, a diuretic, and betahistine. If patients failed medical therapy, based upon their inadequate vertigo control and subjective impact on their quality of life, then they were considered candidates for ablative therapy. Patients willing to proceed with ablative therapy were offered IT Dex as an initial alternative.

Inclusion criteria included definite unilateral Ménière's disease based on AAO-HNS criteria, failed maximal medical therapy, and progression to IT Dex as an alternative to ablative treatment. Exclusion criteria included bilateral Ménière's disease, less than 1 year follow-up, other concurrent or previous inner ear disease, previous ear surgery (other than a tympanostomy tube), previous IT Gent treatment, and previous oral or IT steroids for Ménière's disease. A total of 106 consecutive patients were included in the analyses.

Intratympanic Dexamethasone Therapy

Patients were observed in the clinics of the two senior authors (L.S.P. and S.K.A), and each clinic used their preferred IT Dex protocol consistently throughout the study. Although patients were not formally randomized between the two clinics, the investigators were not involved in screening referrals or booking patients (Table 1).

L.S.P performed one initial IT Dex injection, and repeated future single injections if the patient had poor vertigo control or recurrent symptoms after initial control. The patient was positioned supine, with the head turned away from the affected ear and the neck fully extended. Topical phenol 15% solution prepared on site in our pharmacy was applied to small regions of both the anterior and posterior tympanic membranes (TM). A 26-gauge spinal needle on a 1 cc tuberculin syringe was first used to make an anterior superior ventilation hole, and then the needle was inserted through the mid-posterior region. The middle ear was filled with preservative-free dexamethasone solution (10 mg/ml). After 10 minutes, the middle ear was refilled with Dexamethasone solution (10 mg/ml) through the same injection site in the posterior TM. The patient was kept supine for an additional 10 minutes, for a total of 20 minutes of treatment time. The patient was then discharged from clinic and scheduled for follow-up in 1 to 2 months.

S.K.A. performed an initial series of four injections of IT Dex over a 4-week period, and repeated future single or series of injections if the patient had recurrent vertigo after initial control. The patient was positioned supine, with the head turned away from the affected ear. The same topical phenol solution was applied to the posterior inferior quadrant of the TM, and a myringotomy was performed. Dexamethasone solution (10 mg/ml) was instilled through the myringotomy to fill the middle ear. After 10 minutes, the ear was rechecked and if needed the middle ear was refilled with dexamethasone solution (10 mg/ml) through the myringotomy. The patient was kept supine for an additional 10 minutes, for a total of 20 minutes of treatment time. After this, a Baxter beveled button ventilating tube was placed in the myringotomy. At the second, third, and fourth injections, Dexamethasone solution (10 mg/ml) was injected into the middle ear through the tube and the patient received the same 20 minutes total treatment time. After the fourth injection, the tube was removed, and the myringotomy allowed to heal. Follow-up was scheduled in 1 to 2 months.

TABLE 1. *Demographic data for the two protocol populations (pure-tone average [PTA])*

	Average Age (yr)	Males	Females	PTA Avg (dB)
Single	54.9	25	27	45.2
Series	54.1	23	31	47.7

Audiometry

All patients underwent baseline audiometry before IT Dex treatment. Audiograms were repeated after IT Dex therapy, and before consideration of IT Gent. Pure-tone averages (PTA) were calculated as the average of pure-tone thresholds at 0.5, 1, 2, and 3 kHz (if 3 kHz was not tested, threshold at 4 kHz was used to calculate the average).

Statistical Analysis

Survival analysis was performed using Graph Pad Prism, with subgroup analysis performed with the Log-rank (Mantel–Cox) test. Day 0 was set as the date of first IT Dex injection. Length of follow-up was calculated as the number of days between the first injection and the administrative stop date of the study (June 16, 2015). After the administrative stop date, no further data was collected. Failure was defined as the date the patient received their first IT Gent injection or labyrinthectomy (no vestibular nerve sections occurred in this cohort). Audiometric PTAs were compared for patients who did not advance to ablative therapy, using a two-tailed paired *t* test (alpha = 0.05). If the baseline audiogram was not repeated (seven patients), these patients were excluded from this analysis.

RESULTS

Number of Injections

The range of the number of injections of IT Dex in this study was 1 to 29 (Fig. 1). The mean and median number of injections per patient were 3.54 and 3 for L.S.P., respectively, and 8.56 and 8 for S.K.A.

Survival Analysis

Overall, patients were followed for an average of 2 years and 11 months from the date of first IT Dex injection. The range of follow-up times was 29 days to 7.3 years. The shortest follow-up of 29 days was in a patient who did not respond at all to IT Dex and wanted immediate treatment with IT Gent at the first follow-up visit. Survivors (those who did not proceed to IT Gent or labyrinthectomy) were followed for an average of 3.3 years (range: 1.1 –7.3 yr). Among failures (proceeded to IT Gent or labyrinthectomy), the average time to failure was 336 days (range: 29 d to 4.2 yr).

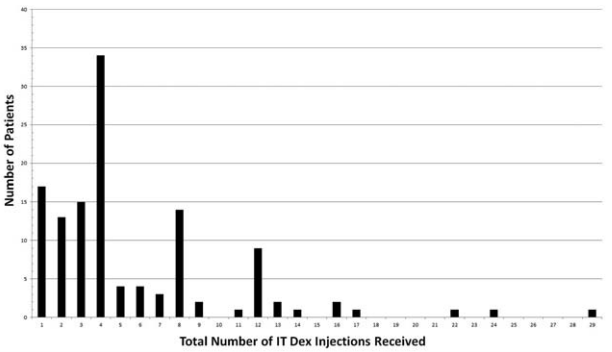

FIG. 1. Distribution of the number of intratympanic dexamethasone injections per patient. Most patients received either one or four injections in total.

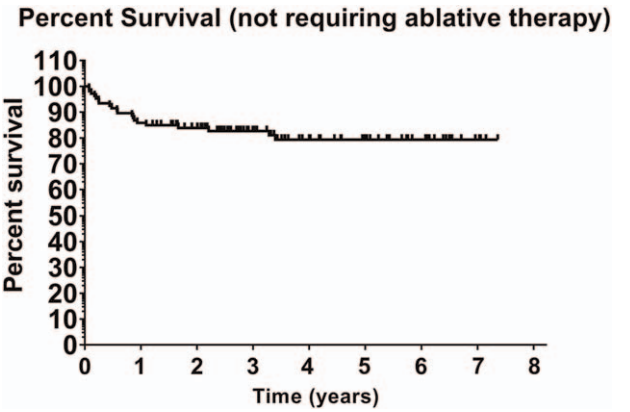

FIG. 2. Kaplan–Meier survival analysis (n = 106) of percent of patients not requiring ablative therapy versus time (in days) since first intratympanic dexamethasone injection. Tick marks represent, for a given patient who did not require ablative therapy, the time from the first intratympanic dexamethasone injection until the administrative stop date of the study.

A Kaplan–Meier analysis was used to evaluate the results, as was done by Boleas-Aguirre et al. (11) in a study of similar design. Based on the survival analysis (Fig. 2), survival at 1, 2, 3, 4, and 5 years was 85.9, 83.9, 82.7, 79.3, and 79.3%, respectively.

Subgroup survival analysis was performed to compare patients treated with the single-injection protocol (n = 52) and those treated with the injection series protocol (n = 54) (Fig. 3). Survival was higher with injection series, but this was not statistically significant ($p = 0.38$).

Audiometric Outcomes

We compared PTA scores from the baseline audiogram (before first IT Dex injection) with the last audiogram before the study administrative stop date. Overall,

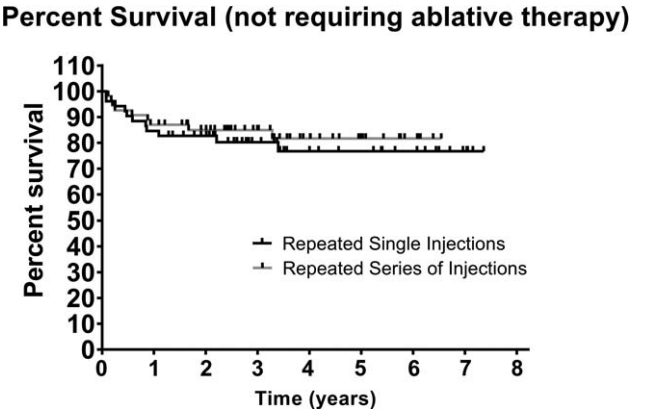

FIG. 3. Kaplan–Meier subgroup survival analysis comparing patients treated with repeated single injections of intratympanic dexamethasone (n = 52) and those treated with repeated series of injections of intratympanic dexamethasone (n = 54) ($p = 0.38$). Tick marks represent, for a given patient who did not require ablative therapy, the time from the first intratympanic dexamethasone injection until the administrative stop date of the study.

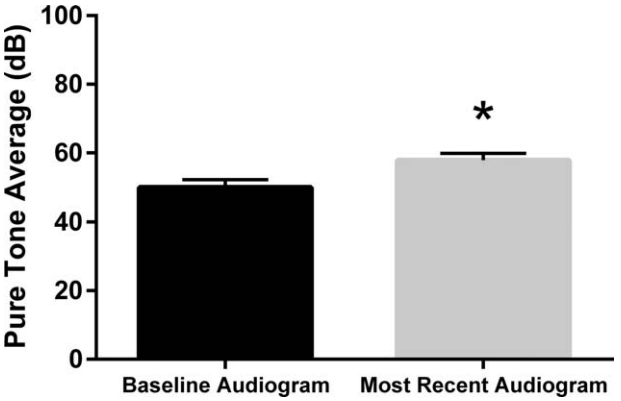

FIG. 4. Comparison of baseline and most recent pure-tone averages (mean ± SEM) for patients who received only intratympanic dexamethasone injection(s) (n = 79). *$p = 0.0000007$.

there was a worsening of PTA scores by an average of 8.27 dB ($p < 0.0001$) (Fig. 4). We also found no significant differences in PTAs between the two protocols (Fig. 5).

Adverse Events

No persistent acute hearing losses were identified based on follow-up audiometry and subjective complaints. The Dex solution was warmed to body temperature before injection to avoid the caloric effect; however, there were occasional cases of transient vertigo during the injection. A small percentage of patients reported mild otalgia during instillation; however, this was also short-lived. No injections needed to be aborted because of these effects. There were no persistent tympanic membrane perforations in either protocol. There were no other adverse events.

DISCUSSION

Synopsis of Key Findings

The previous study by Garduño-Anaya et al. (9) has provided support that IT Dex may provide vertigo control in Ménière's disease. The current study was a prospective review of 106 patients with definite Ménière's disease which compared two different protocols of IT Dex.

Silverstein et al. (13) found that of 50 patients who declined surgery for Ménière's disease, 57% had complete vertigo control at 2 years, 73% had improvement at 2 years, and 71% had complete control after an average of 8.3 years. These numbers are typical of the spontaneous improvement rates reported for Ménière's, which are 60 to 80% over 2 to 8 years (14). Any therapy targeted at control of vertigo spells must be measured against this high spontaneous improvement rate. The rate of avoiding ablative therapy in the current study of 79.3% at 4 years is within the range of the spontaneous improvement rates in the literature. This may indicate that IT Dex provides improved symptom control as a temporizing measure to avoid ablative therapy, but that the disease eventually goes into its own natural remission.

Various dosages and dosing regimens of IT Dex have been reported for Ménière's disease, revealing the difficulty in selecting how to best administer this medication (7). This study compared two dosing strategies (single-injection protocol versus injection series protocol) and demonstrated a 5% better outcome with the series of injections, although this was nonsignificant.

Hearing outcome analysis revealed a small (8.27 dB) but significant decline of PTA in the patients treated with IT Dex. There were no acute hearing losses, and the use of IT Dex did not have a dramatic protective effect. As the average patient was followed for almost 3 years, the natural history of Ménière's disease was likely a significant factor. Sennaroglu et al. (15) similarly found that of 24 Ménière's disease patients treated with IT Dex, 38% had a decrease in hearing level (30% by 10 dB, 8% by 20 dB) during the course of their study. This study did not examine whether IT Dex may offer a hearing protective effect if used in newly diagnosed patients earlier in the course of their disease.

The single patient who received a total of 29 injections warrants further discussion. This patient actually received a total of 7 series of IT Dex over a 4-year period (approximately one series every 7 mo). He achieved symptomatic control after each series and declined to undergo ablative treatment. Interestingly, in the 28-month period after their last injection series, this particular patient went on to develop Ménière's disease in their contralateral ear. This patient highlights a couple of key points of this treatment. First, IT dex can be considered a temporizing measure until the disease naturally burns itself out. Second, preservation of vestibular function in the primary ear is highly desirable in the chance that the contralateral ear becomes affected by Ménière's disease or damaged by other causes.

Strengths of the Study

Strict inclusion and exclusion criteria were used to include patients only with unilateral definite Ménière's disease (AAO-HNS 1995 definition), and to exclude

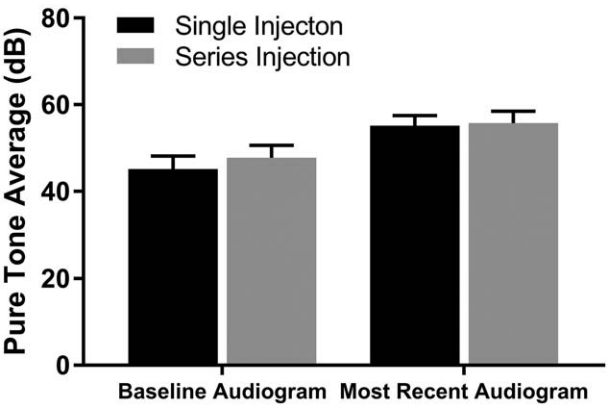

FIG. 5. Comparison of baseline and most recent pure-tone averages (mean ± SEM) with data separated into treatment protocol groups: single injection (n = 47) and series injection (n = 52). No significant difference between groups.

patients who had previously been treated with anything other than medical management, and those with other otologic conditions.

Follow-up for an average of almost 3 years allowed characterization of longer-term control of vertigo attacks with IT Dex. The Kaplan–Meier survival analysis is beneficial in a study of this type where patients have different follow-up lengths. This predicted long-term avoidance of ablative therapy up to 7 years from the initial injection.

A patient-centered definition of treatment success and failure was used. This allowed patients who received benefit from IT Dex to receive it again if symptoms became less well controlled, and it allowed for patients with poor symptom control with IT Dex to proceed to IT Gent or labyrinthectomy. In this manner, the results reflect clinical practice, and represent each patient's satisfaction with the control of their vertigo.

Another strength of this study was the large number of patients who had never been previously treated with oral or IT steroids for their Ménière's disease before being treated at our center. This is largely due to our regional referral patterns from family physicians and general Otolaryngologists to a single-tertiary care center.

Limitations of the Study

The patients were not randomized to the two different treatment arms; however, they were treated based on the treating physician's existing practice protocols. The physicians were not involved in screening referrals or booking patients to reduce selection bias. Another limitation was the inability to use the AAO-HNS Guidelines on vertigo control (2) due to the inadequate length of follow-up. Although the frequency of vertigo attacks was assessed before and after the procedure, only general vertigo control and effect on quality of life could be reported in each of the treatment arms. Finally, no control group was included in this study to examine whether IT Dex has a benefit over placebo. Although this has been studied by other groups, this primary objective of this study was to examine the difference between two different injection protocols.

Comparisons With Other Studies

The methodology of this study largely mirrored the study by Boleas-Auirre et al. (11) in 2008. They performed a similar analysis of their patients with medically refractory unilateral Ménière's disease treated with IT Dex (12 mg/ml) on an ''as needed'' basis and found that of 129 subjects treated with IT Dex, 91% received acceptable vertigo control, and 12 subjects failed and proceeded to IT Gent. Of patients with 2-year follow-up data, 91% had vertigo control with IT Dex. In comparison to the present study, Boleas-Aguirre et al. (11) report a 7% better survival at 2 years (91% versus 83.9%). This small difference may reflect the heterogeneity of symptom control in patients with Ménière's disease. As well, given that both protocols used a patient satisfaction definition of vertigo control, individual patient differences could be significant and could account for the differences in outcomes between the two studies.

A Cochrane review has not been able to establish if IT Dex has a therapeutic effect in Ménière's disease (8). Albu et al. (16) performed a randomized, double-blind study of IT Dex and high-dosage betahistine. They were unable to demonstrate a difference in vertigo control. Furthermore, there is insufficient evidence that betahistine itself has a therapeutic role in the management of vertigo in Ménière's disease (17). Casani et al. (18) performed a randomized controlled trial comparing IT Dex and IT Gent in patients with unilateral Ménière's disease. They found that at 2 years, only 61% of patients treated with IT Dex had complete or substantial control of vertigo, compared with 93.5% of those treated with IT Gent. Their weaker results with IT Dex contrast with the present study, and may be due to the subjective nature of vertigo control given by patients.

Taken together, IT Dex allows ~80 to 90% of patients to avoid ablative therapy. However, despite a study indicating the benefit of IT Dex over placebo (9), additional randomized-controlled trials are needed to completely delineate its clinical efficacy (8).

A recent randomized, double-blind trial published in *The Lancet* compared the effectiveness of IT steroids versus gentamicin in patients with unilateral Ménière's disease. However, the study used methylprednisolone rather than dexamethasone, and as such, it would be difficult to draw any conclusions therein (19).

Clinical Applicability of the Study

IT Dex represents a nonablative therapy offered to Ménière's patients for management of vertigo episodes that do not respond to medical therapy (including low salt diet, diuretics, and betahistine). It likely provides short-term symptomatic control allowing patients to avoid ablative therapy, rather than changing the natural history of the disease. Our data exhibits 5% superior avoidance of ablative therapy using an injection series versus a single injection, which was statistically nonsignificant, and needs to be weighed against the increased cost and inconvenience. The safety profile and lack of adverse events make IT Dex an additional option for patients with bilateral Ménière's disease or those with only hearing/vestibular ears.

REFERENCES

1. Meniere P. On a particular form of serious deafness depending on a lesion of the inner ear [in French]. *Gazette Medicale Paris* 1861;16:29.
2. Committee on Hearing and Equilibrium. Meniere's disease: Criteria for diagnosis and evaluation of therapy for reporting. *AAO-HNS Bull* 1985;5:6–7.
3. Coelho DH, Lalwani AK. Medical management of Ménière's disease. *Laryngoscope* 2008;118:1099–108.
4. Hu A, Parnes LS. 10-year review of endolymphatic sac surgery for intractable Meniere's disease. *J Otolaryngol Head Neck Surg* 2010;39:415–21.
5. Hu A, Parnes LS. Intratympanic steroids for inner ear disorders: A review. *Audiol Neurotol* 2009;14:373–82.

6. Banerjee A, Parnes LS. Intratympanic corticosteroids for sudden idiopathic sensorineural hearing loss. *Otol Neurotol* 2005;26: 878–81.
7. Salt AN, Plontke SK. Principles of local drug delivery to the inner ear. *Audiol Neurootol* 2009;14:350–60.
8. Phillips JS, Westerberg B. Intratympanic steroids for Ménière's disease or syndrome. *Cochrane Database Syst Rev* 2011;7: CD008514.
9. Garduño-Anaya MA, Couthino De Toledo H, Hinojosa-González R, Pane-Pianese C, Ríos-Castañeda LC. Dexamethasone inner ear perfusion by intratympanic injection in unilateral Ménière's disease: A two-year prospective, placebo-controlled, double-blind, randomized trial. *Otolaryngol Head Neck Surg* 2005;133:285–94.
10. Lambert PR, Nguyen S, Maxwell KS, et al. A randomized, double-blind, placebo-controlled clinical study to assess safety and clinical activity of OTO-104 given as a single intratympanic injection in patients with unilateral Ménière's disease. *Otol Neurotol* 2012;33: 1257–65.
11. Boleas-Aguirre MS, Lin FR, Della Santina CC, Minor LB, Carey JP. Longitudinal results with intratympanic dexamethasone in the treatment of Ménière's disease. *Otol Neurotol* 2008;29:33–8.
12. Monsell EM. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Menière's disease. American Academy of Otolaryngology-Head and Neck Foundation, Inc. *Otolaryngol Head Neck Surg* 1995;113:181–5.
13. Silverstein H, Smouha E, Jones R. Natural history vs. surgery for Menière's disease. *Otolaryngol Head Neck Surg* 1989;100:6–16.
14. Pullens B, Verschuur HP, van Benthem PP. Surgery for Ménière's disease. *Cochrane Database Syst Rev* 2013;2:CD005395.
15. Sennaroglu L, Sennaroglu G, Gursel B, Dini FM. Intratympanic dexamethasone, intratympanic gentamicin, and endolymphatic sac surgery for intractable vertigo in Meniere's disease. *Otolaryngol Head Neck Surg* 2001;125:537–43.
16. Albu S, Chirtes F, Trombitas V, et al. Intratympanic dexamethasone versus high dosage of betahistine in the treatment of intractable unilateral Meniere disease. *Am J Otolaryngol* 2015;36:205–9.
17. James AL, Burton MJ. Betahistine for Menière's disease or syndrome. *Cochrane Database Syst Rev* 2001;1:CD001873.
18. Casani AP, Piaggi P, Cerchiai N, Seccia V, Franceschini SS, Dallan I. Intratympanic treatment of intractable unilateral Meniere disease: Gentamicin or dexamethasone? A randomized controlled trial. *Otolaryngol Head Neck Surg* 2012;146:430–7.
19. Patel M, Agarwal K, Arshad Q, et al. Intratympanic methylprednisolone versus gentamicin in patients with unilateral Ménière's disease: A randomised, double-blind, comparative effectiveness trial. *Lancet* 2016;388:2753–62.