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Hearing changes after intratympanic steroids for secondary (salvage) therapy of sudden hearing loss: a meta-analysis using mathematical simulations of drug delivery protocols

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Abstract

Objective—The use of glucocorticoids for secondary (salvage/rescue) therapy of idiopathic sudden hearing loss (ISSHL), including controlled and uncontrolled studies with intratympanic injections or continuous, catheter mediated applications, were evaluated by means of a meta-analysis in an attempt to define optimal local drug delivery protocols for ISSHL.

Study Design—A total of 30 studies with 33 treatment groups between January 2000 and June 2014 were selected based on sufficiently detailed description of application protocols. Cochlear drug levels were calculated by a validated computer model of drug dispersion in the inner ear fluids based on the concentration and volume of glucocorticoids applied, the time drug remained in the middle ear, and on the specific timing of injections. Various factors were compared with hearing outcome, including baseline data, individual parameters of the application protocols, calculated peak concentration ($C_{\max}$), and total dose (Area under the curve, AUC).

Results—There was no dependence of hearing outcome on individual parameters of the application protocol, $C_{\max}$ or AUC. Hearing gain and final hearing thresholds were independent of treatment delay.

Conclusion—Based on the available data from uncontrolled and controlled randomized and non-randomized studies no clear recommendation can be made so far for a specific application protocol for either primary or secondary (salvage) intratympanic steroid treatment in patients with ISSHL. For meta-analyses, change in pure tone average (PTA) may not be an adequate outcome parameter to assess effectiveness of the intervention especially with inhomogeneity of patient populations. Final PTA might provide a better outcome parameter.

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Disclosures:

Stefan K. Plontke is a consultant for Otonomy, Inc., San Diego, USA and chief of the scientific advisory board of AudioCure Pharma GmbH, Berlin Germany.

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Keywords

sudden hearing loss; salvage therapy; rescue therapy; steroids; intratympanic; meta-analysis

Introduction

Local, intratympanic application of glucocorticosteroids (“steroids”) for the treatment of idiopathic sudden sensorineural hearing loss (ISSHL) has become a frequently used therapeutic option for secondary (synonyms: “salvage”, “rescue”, “second line”, “reserve”) treatment, i.e. after failure of hearing improvement with primary (initial) systemic therapy. Results of randomized controlled trials suggest that intratympanic steroid therapy may be superior to systemic or no steroid treatment when used as a secondary intervention (1). A variety of treatment protocols, however, have been used which differ markedly in their key parameters such as drug used, drug concentration and applied volume, number of injections and intervals between injections, total duration for all treatments, and starting time of secondary therapy after onset of ISSHL. No specific optimal application protocol has been established so far and data on the quantitative relationship between the parameters of the application protocols used and improvement of hearing are missing.

When applied to the middle ear cavity, drug is lost by multiple mechanisms so that the available concentration driving entry into the inner ear declines with time. There is volume loss via the Eustachian tube, aided by the ciliated epithelium of the ventral region of the middle ear mucosa (2,3). In addition, drugs may be bound and/or eliminated by the middle ear mucosa. Once the drug has entered the inner ear, it diffuses to fluid and tissue compartments of lower concentration and may be rapidly eliminated (4,5), typically resulting in large basal – apical concentration gradients in scala tympani perilymph (6–9). Therefore, repeated intratympanic injections with short intervals, continuous application via catheter and pumps or controlled release drug delivery systems have been suggested for inner ear drug delivery for indications likes ISSHL (10–12).

In a previous study, we have compared different application protocols quantitatively for primary intratympanic therapy of ISSHL alone or in combination with systemic steroids. Specific parameters of the treatment protocols (e.g. applied concentration, volume, numbers and frequency (interval) of application etc.) and their relation to hearing outcome in these studies were evaluated. In addition, as a synthesis of the variety of parameters for a specific treatment protocol, maximum drug concentration ($C_{\max}$) and total dose (area under the curve, AUC) in the inner ear fluids was calculated by the means of a validated computer model and evaluated with respect to their influence on hearing outcome (13).

The aim of this study was to evaluate the effect of different application protocols in secondary (salvage) treatment of ISSHL on hearing outcomes and – if possible – and to provide recommendations for optimal treatment protocols.

Materials and Methods

Data Sources and Study Selection

For literature research PubMed and GoogleScholar were used to identify clinical studies on intratympanic steroids for secondary treatment of ISSHL. Prospective and retrospective, randomized and non-randomized, controlled and non-controlled studies were included. Only treatment groups utilizing single or repeated injections or continuous application via a round-window-catheter were considered. Studies using the MicroWick (14) were not included in the evaluation, since the pharmacokinetics of this method are yet unknown.

Further inclusion criteria were: Used drug must be dexamethasone or methylprednisolone, the mean of hearing loss in treatment groups before start of local treatment (PTA before) must not exceed 90 dB HL, and the delay between onset of ISSHL and start of secondary treatment must be shorter than 10 weeks (70 days).

Published studies between January 2000 and June 2014 were then selected based on description of treatment protocols with respect to drug concentration, application time, dosing regimen (i.e. start, number, total time and timing of intervals of treatments), and outcome parameters (change of hearing thresholds, i.e. hearing gain). Parameter description must have been in sufficient detail to permit analysis with the computer model. If some of the relevant information were not provided in the publications, the authors were contacted.

Calculation of inner ear drug dispersion and synthesis of application parameters

A computer model of drug dispersion in the inner ear fluids (Washington University Cochlear Fluids Simulator, Version 3.082, <http://otocore.wustl.edu/saltlab/CochlearFluidsSimulator.aspx>) was used to calculate the distribution of steroid with time in the perilymph of scala tympani. The computer model has been validated for a number of steroids by comparison with measured data from guinea pigs (4,7,9,15–17) and from humans (5,18,19). Details of the simulations and their parameters have been described previously (13).

Briefly, based on parameters of the application protocol, the maximum concentration ($C_{\max}$) and the total dose (area under the curve, AUC) of the drug in the cochlear segment corresponding to the 500 – 4000 Hz region (20), the typical frequency range used for the pure tone average (PTA) in most of the studies, were calculated.

For treatment protocols with multiple injections, total dose (AUC) was calculated for a single injection, and multiplied by the number of injections during therapy. For treatment protocols using a continuous application via the round window catheter simulations were run over 24 hours since a maximum steady state concentration is reached within this time period. The AUC increased linearly beyond this time point.

Statistical evaluation

Dosing in the cochlea ($C_{\max}$ and AUC) and parameters of the delivery protocol, and demographic data were evaluated with respect to mean change of hearing thresholds (“PTA hearing gain”) and mean final threshold (“Final PTA”). For statistical evaluation with a

linear regression analysis, the software GraphPad Prism 5.02 (GraphPad Software, La Jolla, USA) was used. In this linear regression analysis each point on the graph isn't a single patient, but the summary of subjects (mean) from a treatment group in a study. In order to account for study size and within-study variance an additional meta-regression analysis was performed with SPSS 22 (IBM, Armonk, USA). However, this meta-regression analysis could only consider the subpopulation of treatment groups where standard deviation of PTA hearing gain was reported (15 of 28 studies [54%]).

Results

A total of 30 studies with 33 treatment groups were included in the analysis (figure 1). Characteristics, extracted parameters of the application protocols, and calculated maximum intracochlear drug concentrations of each selected study group are detailed in tables 1 and 2.

For secondary therapy of ISSHL, neither the change in hearing (hearing gain) nor the final hearing threshold depended on individual parameters of the application protocol or on demographic factors. Specifically, there was no dependence of hearing gain on the drug used (dexamethasone or methylprednisolone) (figures 2a, b), the number of injections (figure 2c), the frequency of injections (figure 2d), the estimated time the drug remained in the middle ear (figure 2e), the total duration of treatments (figure 2f), the time of the endpoint measurement (figure 2g) or on the age of patients (figure 2h). Similar results were found when final hearing threshold was used as an outcome measure rather than hearing change (data not shown).

After synthesis of the individual parameters of the treatment protocols by the means of the computer model for calculating intracochlear drug concentration ($C_{\max}$) and total dose (AUC) for each therapy group, no effects on hearing outcome for either, dexamethasone (figures 3a, b) or methylprednisolone (figure 3c, d) were found.

Hearing improvement significantly correlated with the amount of hearing loss before commencing secondary (salvage) therapy ($R^2=0.17$, $p=0.027$, figure 4b). Final hearing threshold also correlated significantly with initial hearing loss, with poorer prognosis for more severe hearing loss before start of secondary therapy ($R^2=0.21$, $p=0.012$, figure 4d). Both, hearing gain and final hearing threshold were found to be independent of the delay before starting secondary therapy (figures 4a, c).

Table 3 shows the results of the meta-regression analysis among primary intratympanic treatment protocols (13). As in the linear regression analysis, hearing improvement correlated with the amount of hearing loss before treatment ($p=0.0007$). Table 4 shows the results of the meta-regression analysis for secondary intratympanic treatment protocols. Although, due to incomplete reporting of outcome data, only approximately half of the studies could be included into the meta-regression analysis, the results were almost completely consistent with the linear regression analysis. Hearing improvement correlated with the level of hearing loss before treatment ($p=0.022$). In addition, mean age of patients negatively correlated with the mean hearing improvement ($p=0.016$). The duration between injections showed a positive correlation with hearing gain ($p=0.029$), with studies with less

frequent injections resulting in better mean hearing improvement, which seems counterintuitive.

Discussion

In the presented analyses, we found no impact of individual parameters of the treatment protocols on mean hearing outcome in studies with intratympanic steroid application as secondary therapy for ISSHL (figure 2). This is similar to findings in primary therapy of ISSHL with intratympanic steroid application (13).

After addressing the differences between study protocols by means of a computer model calculating intracochlear maximum drug concentration ($C_{\max}$) and total dose (AUC) in order to enable better comparison of studies, neither of the two calculated measures showed a correlation with treatment success (figure 3).

The calculated intracochlear maximum drug concentrations ($C_{\max}$) reached with treatment protocols using intratympanic injections for secondary therapy of ISSHL were in a similar range as the $C_{\max}$ in primary therapy studies (figure 3a, 3c) (13). In the treatment protocols using continuous application via a round window catheter, estimated cochlear drug concentrations were higher (dexamethasone: 0.36 µg/ml, methylprednisolone: 0.39 – 0.61 µg/ml). However, no “concentration-response” or “dose-response” effects (calculated intracochlear $C_{\max}$ and AUC and correlation with hearing change and final hearing threshold) could be found in the linear-regression and the meta-regression analyses.

In a retrospective cohort study by Alexander et al. (2015), which was published after our analysis (inclusion period for studies was until 2014) including 37 patients separated into two groups, with either 10 or 24 mg/mL dexamethasone phosphate for primary intratympanic therapy of ISSHL, a dose response was reported (51). However, when considering the means of the initial hearing threshold (baseline hearing loss), both, the high and the low dose group in this study, showed a hearing improvement below the average and also a worse final PTA in comparison to all previously analyzed studies (13), (Figure 5a, b).

As discussed in detail in the analysis on primary treatment of ISSHL, it is possible that the concentrations achieved in the PTA range commonly considered as clinically relevant are too low for therapeutic effects at least in protocols using intratympanic injections (13). On the other hand, according to investigations of relative upregulation of genes depending on the activation of glucocorticoid and mineralocorticoid receptors, the estimated intracochlear drug concentrations may have been sufficient to achieve drug mediated changes at the gene regulation level (table 5).

In contrast to primary therapy for ISSHL using intratympanic steroids, in secondary (salvage) therapy there was no tendency for a dependence of hearing gain on the delay of treatment (figure 4a). This is in accordance with the findings of Belhassen and Saliba (53), and appears of clinical importance. Based on this data, no recommendation for the time of initiation of a secondary therapy can be derived so far, at least not for the time period of two to five weeks after start of secondary therapy, for which data are available. In primary therapy, the tendency towards better hearing improvement with earlier start of treatment was

attributed to spontaneous recovery, because the mean initial hearing loss of patients in studies with an earlier start of treatment was also larger, and a larger mean initial hearing loss was also correlated to a larger mean hearing gain (13). If final hearing thresholds were chosen as the outcome parameter instead of hearing change there was no dependency on delay of treatment in both, primary and secondary treatment strategies (figure 4c) (13).

Similar to studies with primary intratympanic therapy, a correlation between hearing loss before treatment and hearing gain was found in studies with secondary therapy, although the correlation was less pronounced (figure 4b). If final PTA was used as the outcome parameter, it was nearly independent from PTA before treatment in primary treatment protocols, whereas in secondary therapy there was a clear worsening of the prognosis with increasing hearing loss before treatment (figure 4d).

This relationship is clearly seen if mean hearing gain, mean hearing threshold before therapy, and mean final PTA of each treatment group are plotted in one diagram and groups are arranged by increasing mean PTA before treatment. Figure 6 compares results from primary and secondary intratympanic treatment groups. In secondary therapy the final PTA decreases more strongly with increasing PTA before therapy because the compensation of more severe hearing loss by increasing hearing gain is less pronounced than in primary treatment. We have previously suggested that this compensating effect in primary therapy for ISSHL is most likely due to spontaneous recovery (13). In secondary therapy, i.e. a certain time period after the occurrence of sudden hearing loss, the influence of spontaneous recovery on hearing gain is expected to be less than in primary treatment. In most patients, a large proportion of spontaneous recovery is expected to be completed within the first days after onset of ISSHL, whereas a secondary treatment mostly starts after approximately two weeks (figure 4a).

Unlike in a previous meta-analysis of the dependence of hearing changes on the dose of intratympanically applied gentamicin (for the treatment of Menière's disease) using mathematical simulations of clinical drug delivery protocols, where detailed data were available for almost 600 individual patients (18), here we were facing studies where only summary data of patient groups were available. Although, in many studies reporting was incomplete, we performed a meta-regression analysis based on those studies, where standard deviations of mean outcome measures were provided (15 of 28 studies [54%]). The meta-regression analysis, which accounts for study size and within-study variance (table 4), confirmed almost all results of the linear regression analysis, especially the correlation between mean hearing gain and the level of mean hearing loss before treatment. In the meta-regression analysis, however, mean older age correlated with poorer hearing improvement. This observation has often been reported before, i.e. older age being a negative prognostic factor for hearing improvement. In addition, longer durations between injections seem to be related with better hearing improvement which is not seen in the linear regression analysis (figure 2d). However, this observation appears less plausible, since related parameters, like duration of treatment or total numbers of injections, did not show this correlation with hearing gain. Therefore, and since the meta-regression, due to incomplete reporting, represents a much smaller subset of studies (approximately 50%), this observation might be false positive.

For the above reasons, data from studies with primary intratympanic treatment were re-analyzed with the same meta-regression analysis method, and confirmed the previously described observations (table 3) (13).

Randomized controlled trials with limited numbers of patients suggested the efficacy of intratympanically applied glucocorticoids as a salvage treatment for ISSHL and meta-analyses based on these clinical studies supported these conclusions (54–56). However, in clinical studies with small numbers of patients there is a higher risk that heterogeneity, e.g. through imbalances between treatment groups influence the outcome of the study. There are several conditions which might lead to imbalance between treatment arms. As the timing of the observation period appears critical, even small differences between groups could significantly influence the result (13,57). In some patients, spontaneous recovery only starts after a couple of days or even weeks (58–60). In these patients, impact of spontaneous recovery on hearing gain will not play a role during primary therapy but only during secondary therapy. In addition, different types of hearing loss (shape of audiogram) are associated with different degrees of spontaneous recovery (58,61–63). But these specific audiogram types are not adequately considered by simply assessing a pure tone average (PTA), e.g. from 0.5 to 4 kHz (64). The degree and time course of spontaneous recovery in patients seems to vary in individual patients. Therefore, balancing of treatment arms, especially in non-randomized trials or trials with small numbers of patients is challenging. However, there is no guarantee for balanced treatment groups in randomized controlled trials per se. Randomization only leads to balanced treatment arms with adequately large numbers of patients. Additional symptoms like vertigo may influence the degree of spontaneous recovery independent from the initial amount of hearing loss (65–67). Cinamon and colleagues showed in their randomized controlled trial, that hearing gain in one treatment arm tended to be worse than in the other, because in this group more patients were included with accompanying vertigo (68). Finally, ISSHL is – by definition – an idiopathic condition. Therefore, it is not obvious whether or not patients with different (unknown) causes for ISSHL despite similar parameters like hearing thresholds before treatment are grouped together (56,58). The influence of number of patients in a clinical study on variation of outcome is demonstrated in figure 5c and 5d. A tendency for decrease of variation in outcome is found with increasing group size in primary as well as in secondary treatment strategies. Therefore, studies with large numbers of patients are necessary to permit well-founded conclusions. If only studies with small numbers of patients are accessible or possible, then it is of even more importance to publish individual patient results to make them available for meta-analyses.

Limitations of this meta-analysis on secondary therapy of ISSHL with intratympanic steroids are the same as in a previous meta-analysis on primary treatment strategies and similar to other meta-analyses on ISSHL. 1) There was no uniform scheme for audiological evaluation in the selected studies, i.e. outcome parameters differed at least slightly. 2) Due to the lack of individual patient data in the published studies (13,64), each point on graphs of the linear regression analysis represents a summary of a treatment group instead of an individual patient. Based on the methodological limitations of such a summary-level analysis, it is difficult to make firm subject-level conclusions. 3) While the patient number and standard deviation could not be considered in the linear regression analysis,

incorporating these factors in the meta-regression analysis resulted in exclusion of 14 of 28 (56%) studies, introducing selection bias.

Conclusions

Based on the available data from uncontrolled and controlled randomized and non-randomized studies no clear recommendation can be made so far for a specific application protocol for either primary or secondary (salvage) intratympanic steroid treatment in patients with ISSHL.

Both, hearing gain and final hearing threshold, were found to be independent on the delay before start of secondary (salvage) therapy.

For meta-analysis of studies on ISSHL with an inherent inhomogeneity of patient populations and baseline parameters (e.g. initial averaged hearing loss and start of treatment), hearing improvement (change of hearing threshold or PTA hearing gain), may not be an adequate outcome parameter to assess effectiveness of the intervention. Evaluation of final hearing threshold might be used as a better alternative.

Further efforts should be made towards the compliance with existing recommendations on outcome parameters and the improvement of minimum reporting standards in clinical studies on idiopathic sudden sensorineural hearing loss including the publication of demographic and baseline data and outcomes in individual patients.

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Figure 1.

Flowchart of the study selection process. IT = intratympanic, Dex = dexamethasone, MP = methylprednisolone.

Figure 2.

Dependence of change in pure tone average (PTA hearing gain) on: (a) dexamethasone concentration used for the injection (IT) or continuous application through an implanted catheter, (b) methylprednisolone concentration used for the injection (IT) or continuous application through an implanted catheter, (c) total number of injections. Continuous application through an implanted catheter is referred to continuously (cont.) on x-axis. Single injections through an implanted catheter is plotted by their number of injections on x-axis. (d) frequency of injections. Continuous application through an implanted catheter is referred to continuously (cont.) on x-axis. Single injections through an implanted catheter is plotted by the days between injections. (e) application time during injection. For continuous application the application time is referred to the whole duration of treatment. For single injections through an implanted catheter the application time is referred to the duration of a single injection, (f) duration of treatment, (g) time of endpoint measurement, (h) age of patients. * = groups with continuous application are excluded from regression analysis.

Figure 3.

Dependence of change in pure tone average (PTA hearing gain) on the calculated maximum intracochlear drug concentrations ($C_{\max}$) or total doses (AUC) in scala tympani within the range corresponding to the 500 – 4000 Hz region: (a) dexamethasone $C_{\max}$, (b) dexamethasone total dose (AUC), (c) methylprednisolone $C_{\max}$, (d) methylprednisolone AUC.

Figure 4.

Dependence of change in pure tone average (PTA hearing gain) on: (a) the start of treatment (treatment delay) after onset of ISSHL, (b) hearing threshold (PTA) at the beginning of treatment. Dependence of the final hearing threshold (final PTA) on: (c) the start of treatment (treatment delay) after onset of ISSHL, (d) hearing threshold (PTA) at the beginning of treatment.

Figure 5.

A and B: Mean hearing change (a) and mean final hearing threshold (b) for primary therapy of ISSHL from a previous analysis (13) and data from a more recent study suggesting a concentration effect (triangles) (51). C and D: Dependence of the average final hearing threshold (final PTA) on group size for primary (c) (13), and secondary (d) treatment.

Figure 6.

Dependence of change in pure tone average (PTA hearing gain) and final hearing threshold (final PTA) on hearing threshold at the beginning of ("PTA before") primary (a) and secondary (b) treatment of ISSHL (see figure 4b, 4d; figure 5a taken from Liebau et al. 2017 (13), with permission, © Otolology & Neurotology - Wolters Kluwer Health, 2017). PTA hearing gain, final PTA, and PTA before treatment of each group are arranged at the y-axis and study results are sorted by increasing PTA before treatment on the x-axis. In primary therapy (a) larger hearing loss at start of therapy is compensated by higher hearing gain resulting in similar final hearing thresholds (final PTA) with a tendency for a poorer prognosis with larger hearing loss before treatment. In secondary treatment (b) final hearing thresholds decreases more strongly with increasing PTA before because the compensation by increasing hearing gain is less pronounced.

Table 1

Individual study groups characteristics and pure tone audiometry outcome measures for secondary (salvage) therapy of ISSHL. IT = intratympanic, SD = standard deviation, * = additional hyperbaric oxygen therapy (HBO), n.a. = not available, PTA = pure tone average.

Study	Type of study	Treatment	Number of patients	Age	[days]			PTA type	PTA frequencies	Timepoint of measured final PTA after start of treatment [days]		
					Mean	SD	Mean			Mean	SD	SD
Chou et al. 2013 (21)	retrospective	IT	30	48.5	14.9	32.4	n.a.	4 PTA	500, 1000, 2000, 4000	40	n.a.	n.a.
Choung et al. 2006 (22)	prospective	IT	33	39.3	n.a.	33.45	n.a.	4 PTA	500, 1000, 2000, 3000	19	n.a.	n.a.
Cvorovic et al. 2013 (23)	prospective	IT	25	47.3	10.8	< 28	n.a.	5 PTA	250, 500, 1000, 2000, 4000	13	n.a.	n.a.
Dallan et al. 2006 (24)	prospective	IT	9	56.56	n.a.	34.3	n.a.	4 PTA	500, 1000, 2000, 3000	30	n.a.	n.a.
Dallan et al. 2010 (25)	retrospective	IT	27	56.5	15.6	20.5	29.8	4 PTA	500, 1000, 2000, 3000	31	n.a.	n.a.
Dispenza et al. 2013 (26)	prospective	IT	36	n.a.	n.a.	24.3	23.9	n.a.	n.a.	189	n.a.	n.a.
Gouveris et al. 2005 (27)	prospective	IT	40	53.4	n.a.	n.a.	n.a.	11 PTA	125, 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000, 8000	n.a.	n.a.	n.a.
Herr and Marzo 2005 (28)	retrospective	IT(RW catheter)	3	n.a.	n.a.	67.7	n.a.	3 PTA	500, 1000, 2000	53	n.a.	n.a.
Herr and Marzo 2005 (28)	retrospective	IT(RW catheter)	2	n.a.	n.a.	26.25	n.a.	3 PTA	500, 1000, 2000	124	n.a.	n.a.
Ho et al. 2004 (29)	prospective	IT	15	46.1	19.9	29.7	n.a.	6 PTA	250, 500, 1000, 2000, 4000, 8000	45	n.a.	n.a.
Hunchaisri et al. 2010 (30)	prospective	IT	14	45.6	16.2	n.a.	n.a.	3 PTA	500, 1000, 2000	45	n.a.	n.a.
Kakehata et al. 2011 (31)	retrospective	IT	24	46	18.7	15.3	6.4	5 PTA	250, 500, 1000, 2000, 4000	36	n.a.	n.a.
Killic et al. 2007 (32)	prospective	IT	19	52.6	17.7	37.7	n.a.	n.a.	500 – 4000	n.a.	n.a.	n.a.

Study	Type of study	Treatment	Number of patients	Age	Delay onset-treatment [days]		PTA type	PTA frequencies	Timepoint of measured final PTA after start of treatment [days]	
					Mean	SD			Mean	SD
Kopke et al. 2001 (33)	prospective	IT(RW catheter)	4	51.5	n.a.	31.5	n.a.	4 PTA	500, 1000, 2000, 3000	n.a.
Lee et al. 2011 (34)	prospective	IT	21	44	16.2	17.1	5.6	4 PTA	500, 1000, 2000, 3000	56
Lee et al. 2008 (35)	prospective	IT	34	49.9	13.7	34.6	n.a.	4 PTA	500, 1000, 2000, 4000	26
Lefebvre et al. 2002 (36)	prospective	IT(RW catheter)	6	n.a.	n.a.	n.a.	n.a.	n.a.	250 – 3000	15
Li et al. 2011 (37)	prospective	IT	24	53.5	n.a.	n.a.	n.a.	4 PTA	500, 1000, 2000, 4000	60
Moon et al. 2011 (38)	prospective	IT	66	50.3	17.52	18.64	n.a.	4 PTA	500, 1000, 2000, 3000	81
Plaza and Herraiz 2007 (39)	prospective	IT	9	n.a.	n.a.	n.a.	n.a.	4 PTA	500, 1000, 2000, 3000	45
Plontke et al. 2005 (40)	retrospective	IT(RW catheter)	5	39.8	n.a.	n.a.	n.a.	4 PTA	500, 1000, 2000, 3000	43
Rauch et al. 2011 (41)	prospective	IT	67	n.a.	n.a.	n.a.	n.a.	4 PTA	500, 1000, 2000, 4000	72
Raymundo et al. 2010 (42)	prospective	IT	14	43.79	4.46	16.86	1.29	3 PTA	500, 1000, 2000	12
Roebuck and Chang 2006 (43)	retrospective	IT	31	53.5	14	n.a.	n.a.	n.a.	n.a.	8
She et al. 2010 (44)	prospective	IT (microcatheter)	26	48.5	14.2	43.6	49.5	6 PTA	250, 500, 1000, 2000, 4000, 8000	100
Slatery et al. 2005 (45)	prospective	IT	20	52.6	15	< 34	n.a.	4 PTA	500, 1000, 2000, 3000	42
Wang et al. 2012 (46)	retrospective	IT	23	46.2	13.3	n.a.	n.a.	4 PTA	500, 1000, 2000, 4000	37
Wang et al. 2012 (46)	retrospective	IT(RW catheter)	21	47.8	11.3	n.a.	n.a.	4 PTA	500, 1000, 2000, 4000	37
Wu et al. 2011 (47)	prospective	IT	27	49.1	14.2	21.4	1.6	4 PTA	500, 1000, 2000, 4000	43
Xenellis et al. 2006 (48)	prospective	IT	19	50.9	n.a.	n.a.	n.a.	4 PTA	500, 1000, 2000, 4000	60

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Study	Type of study	Treatment	Number of patients	Age	Delay onset-treatment		PTA type	PTA frequencies	Timepoint of measured final PTA after start of treatment [days]	
					Mean	SD			Mean	SD
Yang et al. 2013 (49)	retrospective	IT	35	49.71	15.43	34	n.a.	4 PTA	500, 1000, 2000, 4000	37 n.a.
Yang et al. 2013 (49)	retrospective	IT*	19	44.68	16.04	34	n.a.	4 PTA	500, 1000, 2000, 4000	37 n.a.
Zhang et al. 2012 (50)	prospective	IT	39	51.5	15.7	17	8	5 PTA	250, 500, 1000, 2000, 4000	15 n.a.

Extracted parameters of the application protocols for individual study groups, calculated inner ear drug concentrations, and hearing threshold (PTA) before and after treatment. Dex = dexamethasone, MP = methylprednisolone, cont. = continuous, SD = standard deviation, n.a. = not available, PTA = pure tone average.

Table 2

Study	Drug used	Drug concentration [µg/ml]	Application time [min]	Total # of injections	Frequency of injections [days]	Duration of treatment [days]	C _{max} [µg/ml]	AUC [µg*s/ml]	PTA before		PTA hearing gain		Final PTA	
									Mean	SD	Mean	SD	Mean	SD
Chou et al. 2013 (21)	Dex	4000	20	4	3.5	12	0.011	11.83	68.8	16	10.7	9.8	58.1	n.a.
Choung et al. 2006 (22)	Dex	5000	40	4	3.5	12	0.028	29.36	72	23.4	9.1	n.a.	62.9	22.5
Cvorovic et al. 2013 (23)	Dex	4000	30	4	4	13	0.017	17.67	68.84	n.a.	19.49	n.a.	49.35	n.a.
Dallan et al. 2006 (24)	MP	20000	25	1	n.a.	1	0.018	4.878	85.2	n.a.	24.3	n.a.	60.9	n.a.
Dallan et al. 2010 (25)	MP	20000	30	1	n.a.	1	0.022	5.85	79.9	21.4	19.3	n.a.	60.6	24.9
Dispenza et al. 2013 (26)	Dex	4000	20	5	2	9	0.011	14.79	59.6	n.a.	12.8	15.2	46.8	17.9
Gouveris et al. 2005 (27)	Dex + Hyaluronic acid	4000	20	2.7	2	5	0.011	7.99	70.23	n.a.	12.13	n.a.	58.1	n.a.
Herr and Marzo 2005 (28)	Dex	10000	15840	cont.	cont.	11	0.36	4741.38	72	n.a.	18.3	n.a.	53.7	n.a.
Herr and Marzo 2005 (28)	MP	62500	18720	cont.	cont.	13	0.61	9391.82	88	n.a.	24	n.a.	64	n.a.
Ho et al. 2004 (29)	Dex	4000	30	3	7	15	0.017	13.25	81.04	13.23	28.39	23.14	52.65	27.74
Hunchaisri et al. 2010 (30)	Dex	4000	30	1.2	7	8	0.0167	5.3	63.55	n.a.	9.05	n.a.	55.1	n.a.
Kakehata et al. 2011 (31)	Dex	4000	30	8	1	8	0.017	35.34	74.6	15.3	16.8	21.6	57.8	n.a.
Killic et al. 2007 (32)	MP	62500	15	5	3	13	0.035	45.78	65.2	17.9	18.9	n.a.	46.3	11.3
Kopke et al. 2001 (33)	MP	62500	20160	cont.	cont.	14	0.61	10114.27	84.4	n.a.	49.4	n.a.	35	n.a.
Lee et al. 2011 (34)	Dex	5000	30	4	3.5	12	0.021	22.086	74.6	25.2	11.4	n.a.	63.2	25.6
Lee et al. 2008 (35)	Dex	5000	30	4	3.5	12	0.021	22.087	65.8	23	8.2	11.5	57.6	22
Lefebvre et al. 2002 (36)	MP	62500	14400	cont.	cont.	10	0.61	7224.48	73.53	n.a.	21.63	n.a.	51.9	n.a.

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Study	Drug used	Drug concentration [µg/ml]	Application time [min]	Total # of injections	Frequency of injections [days]	Duration of treatment [days]	C _{max} [µg/ml]	AUC [µg*s/ml]	PTA before		PTA hearing gain		Final PTA	
									[dB HL]		[dB HL]		[dB HL]	
									Mean	SD	Mean	SD	Mean	SD
Li et al. 2011 (37)	MP	20000	45	4	3	10	0.033	35.084	60.7	12	7.8	9.7	52.9	13.7
Moon et al. 2011 (38)	Dex	5000	30	5	2	9	0.021	27.61	80.6	25.38	14.3	19.13	66.3	27.2
Plaza and Herraiz 2007 (39)	MP	20000	15	3	7	15	0.011	8.79	73.3	20.8	33	12.55	40.2	17.3
Plontke et al. 2005 (40)	MP	40000	31680	cont.	cont.	20	0.39	10172.083	86.4	n.a.	12	n.a.	74.4	n.a.
Rauch et al. 2011 (41)	MP	40000	30	4	3.5	12	0.044	46.81	n.a.	n.a.	26.8	n.a.	n.a.	n.a.
Raymundo et al. 2010 (42)	MP	40000	30	3	2	5	0.044	35.11	65.71	8.38	24.76	n.a.	40.95	8.31
Roebuck and Chang 2006 (43)	Dex	24000	20	1	n.a.	1	0.067	17.75	n.a.	n.a.	12	8	n.a.	n.a.
She et al. 2010 (44)	MP	40000	30	10	1	10	0.044	117.033	83.2	12.9	16.7	15.9	66.5	n.a.
Slattery et al. 2005 (45)	MP	56250	30	4	3.5	12	0.062	65.83	82.9	27.2	5.5	n.a.	77.4	28.3
Wang et al. 2012 (46)	Dex	5000	30	4	2	7	0.021	22.086	71	24.2	8.6	n.a.	61	18.7
Wang et al. 2012 (46)	Dex	5000	60	14	0.5	7	0.041	304.39	71	25.2	9	n.a.	62	21.7
Wu et al. 2011 (47)	Dex	4000	20	4	4	13	0.011	11.83	64.6	17.7	9.7	8.5	54.9	20.34
Xenellis et al. 2006 (48)	MP	40000	30	4	4.5	15	0.044	46.81	70.1	20.92	14.9	17	55.1	18.31
Yang et al. 2013 (49)	Dex	5000	30	4	3.5	12	0.021	22.086	n.a.	n.a.	18.87	21.66	n.a.	n.a.
Yang et al. 2013 (49)	Dex	5000	30	4	3.5	12	0.021	22.086	n.a.	n.a.	22.5	18.7	n.a.	n.a.
Zhang et al. 2012 (50)	Dex	5000	30	4	2	7	0.021	22.087	62.9	28.2	13.7	18	49.2	n.a.

Table 3

Results of the meta-regression analysis among primary treatment protocols with intratympanic injections where standard deviation of PTA hearing gain was reported. Treatment groups were weighted according to the outcome parameter PTA hearing gain [dB].

Effect	Regression coefficient	Standard error	95% confidence interval	p-value
Age of patients	0.1039	0.3639	(−0.6093; 0.8170)	0.7753
Delay onset-treatment [days]	−0.5542	0.5034	(−1.5409; 0.4326)	0.2710
PTA before treatment [dB HL]	0.6592	0.1942	(0.2786; 1.0398)	0.0007 *
Timepoint measured Final PTA [days]	0.0291	0.0366	(−0.0427; 0.1009)	0.4267
Duration of total treatment [days]	0.2779	0.3534	(−0.4148; 0.9706)	0.4317
Total # of injections	0.8372	1.0319	(−1.1852; 2.8597)	0.4172
Frequency of injections [days]	0.5656	0.9168	(−1.2312; 2.3525)	0.5372
Application time [min]	0.1257	0.3257	(−0.5127; 0.7641)	0.6996
Applied drug concentration (Dex) [mg/ml]	0.0009	0.0012	(−0.0014; 0.0031)	0.4646
Applied drug concentration (MP) [mg/ml]	<0.0001	0.0002	(−0.0003; 0.0003)	0.9658
C _{max} 0.5 – 4 kHz (Dex) [µg/ml]	−885.078	2449.271	(−5685.65; 3915.49)	0.7178
AUC 0.5 – 4 kHz (Dex) [µg * s/ml]	1.0721	1.1876	(−1.2555; 3.3997)	0.3666
C _{max} 0.5 – 4 kHz (MP) [µg/ml]	1957.59	1687.30	(−1349.51; 5264.69)	0.2460
AUC 0.5 – 4 kHz (MP) [µg * s/ml]	0.5598	1.0565	(−1.5110; 2.6305)	0.5962

*
p<0.05

Table 4

Results of the meta-regression analysis among secondary treatment protocols with intratympanic injections where standard deviation of PTA hearing gain was reported. Treatment groups were weighted according to the outcome parameter PTA hearing gain [dB].

Effect	Regression coefficient	Standard error	95% confidence interval	p-value
Age of patients	-1.1093	0.4610	(-2.0129; -0.2057)	0.0161 *
Delay onset-treatment [days]	0.0815	0.1683	(-0.2483; 0.4114)	0.6280
PTA before treatment [dB HL]	0.4605	0.2004	(0.0676; 0.8534)	0.0216 *
Timepoint measured Final PTA [days]	-0.0047	0.0379	(-0.0789; 0.0696)	0.9020
Duration of total treatment [days]	0.6344	0.4404	(-0.2288; 1.4977)	0.1497
Total # of injections	0.0060	0.8257	(-1.6123; 1.6244)	0.9942
Frequency of injections [days]	2.1961	1.0027	(0.2308; 4.1614)	0.0285 *
Application time [min]	-0.2177	0.2199	(-0.6486; 0.2132)	0.3220
Applied drug concentration (Dex) [mg/ml]	-0.0001	0.0002	(-0.0004; 0.0003)	0.6736
Applied drug concentration (MP) [mg/ml]	-0.0002	0.0006	(-0.0014; 0.0010)	0.7437
C _{max} 0.5 – 4 kHz (Dex) [µg/ml]	-74.344	483.775	(-1022.54; 873.86)	0.8779
AUC 0.5 – 4 kHz (Dex) [µg [*] s/ml]	1.0721	1.1876	(-1.2555; 3.3997)	0.3666
C _{max} 0.5 – 4 kHz (MP) [µg/ml]	-3330.17	2215.77	(-7673.08; 1012.73)	0.1329
AUC 0.5 – 4 kHz (MP) [µg [*] s/ml]	-0.4114	0.7647	(-1.9102; 1.0875)	0.5906

*
p<0.05

Table 5

Relative upregulation of genes depending on the activation of glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) (52).

	Calculated $C_{\max}$ (500 – 4000 Hz) [$\mu\text{g/ml}$]	GR dependent genes	MR dependent genes
Dexamethasone	0.011 – 0.067	95 – 100%	85 – 95%
Methylprednisolone	0.011 – 0.062	90 – 100%	90 – 100%