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Intratympanic Gentamicin Treatment for Ménière's Disease

Yongchuan Chai and Hongzhe Li

Abstract

Ménière's disease (MD) is an inner-ear disease mostly characterized by frequent spontaneous vertigo and fluctuating sensorineural hearing loss. The main purpose of treatment for MD is to reduce or control the vertigo while maximizing the preservation of hearing. Among the various treatments, one that is effective for refractory MD, intratympanic gentamicin (ITG), relies on its ototoxic property to effectively control the vertigo symptoms of most patients. ITG treatment has relatively few side effects compared with surgically destructive treatments, but it also carries a nonnegligible risk of sensorineural hearing loss. So far, there is no consensus on the dosage and treatment duration of ITG. Most researchers recommend that intratympanic injection of gentamicin is more suitable for patients with unilateral onset and impaired hearing function, who are younger than 65 years old, as well as with frequent and severe vertigo attacks, and ineffective prior conservative treatment. Before an ITG treatment, patients should be adequately informed about the risk of hearing loss, and in order to reduce the risk of deafness, low drug dose and long intervals between injections are recommended. In short, to administer an ITG injection, multiple factors should be comprehensively considered including patient selection, pharmacological mechanism, drug dose, the interval of administration, complications, indications, and contraindications.

Keywords: intratympanic, gentamicin, Ménière's disease, management, aminoglycosides, vertigo, vestibulotoxicity, ototoxicity

1. Introduction

Ménière's disease (MD), also called idiopathic endolymphatic hydrops, is one of the most common causes of dizziness originating in the inner ear. The typical clinical manifestations are frequent spontaneous vertigo, fluctuating sensorineural hearing loss, tinnitus, and/or aural fullness. Vertigo is typically the most debilitating symptom, and control of vertiginous episodes is the primary goal of therapeutic interventions for most patients.

There are numerous available therapeutic options for MD including conservative treatments with dietary modifications, oral medication, procedural treatments with intratympanic therapies, and surgical treatments. A failure of conservative therapy often introduces the need for a more aggressive therapy on the treatment algorithm.

Surgical intervention or intratympanic aminoglycosides can be used in patients with intractable vertigo, which, ideally, should control the vertigo while preserving the hearing level and balance. The side effects of aminoglycosides are well-known. The risks of vestibular and cochlear toxicity are mainly related to types of

aminoglycosides, route of administration, duration of the therapy, total or cumulative dose, individual susceptibility, renal function, patient's age, etc.

In 1948, Fowler [1] first used systemic streptomycin to treat vertigo attacks in patients with intractable MD. The results showed that vertigo attacks could be well controlled, but treatment carried the risks of bilateral vestibulopathy, nephrotoxicity, and unpredictable results. In 1957, Schuknekt [2] may have been the first to use intratympanic streptomycin to alleviate vertigo attacks in patients with unilateral intractable MD, and it was firstly named "chemical labyrinthectomy". Intratympanic gentamicin (ITG) for the treatment of severe vertigo was reported by Lange [3]. The initial approach was complete vestibular ablation to control the vertigo. However, with this approach, the hearing was at a greater risk. Over the past decades, the pharmacological mechanisms of aminoglycosides have been progressively studied in depth and clinical trials have been extensively developed.

At present, intratympanic injection of gentamicin is probably the most effective non-surgical treatment to eradicate vertigo in MD and is gradually gaining popularity in the worldwide. Compared with the treatment regimen decades ago, several modifications for ITG treatment have emerged regarding the concentration of the gentamicin solution, the frequency of injections, and the method of delivery. In this chapter, the history, background, and progression of ITG treatment for MD are discussed, as well as the basic science, therapeutic method, treatment efficacy, indications, contraindications, and complications.

2. History of intratympanic gentamicin

Aminoglycosides are highly potent, broad-spectrum antibiotics and are widely used by various routes of injection to treat serious infections caused by Gram-negative bacteria (e.g., *Pseudomonas aeruginosa*, *Proteus* species, *Escherichia coli*, *Klebsiella-Enterobacter-Serratia* species, and *Citrobacter* species), and are sometimes used as an adjuvant treatment for infections caused by Gram-positive bacteria (e.g., *Staphylococcus* species). The basic chemical structure required for both potency and the spectrum of antimicrobial activity of aminoglycosides is that of one, or several, aminated sugars joined in glycosidic linkages to a dibasic cyclitol. Aminoglycosides act primarily by impairing bacterial protein synthesis through binding to prokaryotic ribosomes [4].

Streptomycin, which was discovered in 1944, is the first aminoglycoside antibiotic in human history and was thereafter marked by the successive introduction of a series of milestone compounds (kanamycin discovered in 1957, gentamicin in 1963, and neomycin in 1970s) which definitively established the usefulness of this class of antibiotics for the treatment of Gram-negative bacillary infections. From the 1960s to 1970s, aminoglycosides were widely used, but due to their serious ototoxicity and nephrotoxicity, their systemic application was limited, and they were gradually fading out of the ranks of first-line drugs. At the beginning, the most common side effect of streptomycin used by intravenous injection was temporary imbalance without vertigo or nystagmus. Higher systemic doses increased the chance of permanent imbalance and, occasionally, deafness. These early observations led to animal and cadaver studies which confirmed the vestibulotoxic and cochleotoxic effects of high-dose streptomycin.

Based on its vestibulotoxicity, streptomycin foremost unveiled its potential in the treatment of vestibular diseases. In 1948, about 4 years after streptomycin was discovered, Fowler [1] first used systemic streptomycin to treat vertigo attacks in patients with intractable MD which was refractory to traditional medical treatment. He and others used between 2 and 4 g of intramuscular streptomycin per day in patients with unilateral or bilateral MD, typically until onset of severe imbalance,

and reported that vertigo attacks could be well controlled without loss of hearing. Often, and especially with higher dosing, vertigo control was accompanied with the troubling symptoms of permanent, severe imbalance, and oscillopsia.

In 1957, Schuknecht [2] may have been the first to use intratympanic streptomycin to alleviate vertigo attacks in patients with unilateral MD that was uncontrolled by traditional medical management. He conceived of this idea after noting that intratympanic formalin will readily pass into the inner ear and prevented post-mortem degeneration of the inner ear membranous structures in patients. He correctly theorized that streptomycin could also pass into the inner ear and devised a cat animal model that demonstrated clinical and pathologic vestibulotoxicity with intratympanic streptomycin. Based on these results, he devised a clinical trial of intratympanic streptomycin administration to patients with uncontrolled unilateral MD. He administered variable amounts of streptomycin (between 0.125 and 0.5 g), either hourly or over 4 hours, over a variable amount of days. The first group of three patients who received 1 or 2 days of treatment achieved only brief control of their vertigo, but did not lose any hearing. Subsequently, an additional group of five patients received streptomycin for 3 days or longer. These patients had permanent resolution of their vertigo episodes, but at the cost of deafening the ear. Schuknecht coined the term “chemical labyrinthectomy” to describe this phenomenon. He concluded that intratympanic streptomycin at the therapeutic dosage failed to preserve hearing, and should only be considered for patients who are not good surgical candidates, but would otherwise be proper candidates for inner ear ablation [2].

With the administration of intratympanic aminoglycosides, chemical ablation of the inner ear via systemic administration of aminoglycosides fell into disfavor due to the side effects of bilateral vestibulopathy, nephrotoxicity, and unpredictable results. However, choosing which kind of aminoglycoside for intratympanic injection has gradually changed. In 1977, Lange [3] appears to be the first to have used IT administration of gentamicin. He reported about 55 patients suffering from severe unilateral MD, seen over a period of 3–10 years. Patients were treated with intratympanic administration of streptomycin or better, gentamicin. The medication was given using a plastic tube inserted behind the annulus within the transmeatal approach, and 0.1 ml gentamicin (earlier streptomycin) was instilled every 5 hours until the first signs of inner ear reaction (nystagmus or vertigo) appeared. In 90% of the cases, vertiginous attacks ceased after therapy, and hearing was preserved in 76%.

Entering the 1990s, intratympanic gentamicin had gained widespread popularity in the treatment of MD. Compared with streptomycin, ITG for treatment of MD provided equivalently excellent vertigo control while showing a lower incidence of hearing loss in early clinical data. Gentamicin gained popularity over streptomycin and gradually came to be the drug of choice for chemical ablation of inner ear.

In 1993, Nedzelski et al. [5] studied 50 patients with unilateral MD by treatment of microcatheter administration of streptomycin over a 5 h treatment, 4 treatments within 48 hours, and the rate of vertigo control was up to 96%; only 24% of his patients experienced various degrees of hearing loss. Although streptomycin was being used in the study, he advocated for using gentamicin instead for its theoretical reduction of cochleotoxicity.

Beck and Schmidt [6] reported on their 10 years of experience with intratympanally applied streptomycin and gentamicin in the therapy of MD. They theorized that the dosage might be a critical factor for hearing preservation with vertigo control. Aminoglycosides could be titrated to impede the secretory epithelium of the vestibular apparatus without destroying the sensory cells, thus achieving vertigo control while maintaining caloric response, that is, vestibulo-ocular reflex. More importantly, risk of deafness could potentially be eliminated. By reducing the dosage delivered and titrating, they were able to achieve excellent rates of vertigo

control (92%) while also achieving respectable hearing preservation rates (15% hearing loss with no cases of deafness).

During the same era, around the early 1990s, two schools of thought emerged in an effort to standardize ITG treatment, dubbed the “shotgun” approach, and the “low-dose” approach. The shotgun approach, championed by Nedzelski and others [5], was characterized by daily IT injections to a fixed endpoint or to a clinical threshold that heralded damage to the inner ear. Proponents of this approach attempted to achieve adequate vestibular ablation for long-term vertigo control. The low-dose approach, championed by Magnusson and others [7], was characterized by weekly IT injections, also to a fixed endpoint or to clinical effect. Proponents of this approach tried to achieve vertigo control while minimizing damage to hearing and potentially preserving the caloric response as well.

Today, intratympanic injection of gentamicin is probably the most effective non-surgical treatment to eradicate vertigo in MD. Yet, it is an ablative method that carries a non-negligible risk of hearing loss. Currently, gentamicin is usually instilled via IT injection or through a tympanostomy tube to the round window niche. These injections are repeated over a variable amount of time, typically between daily to weekly injections, until a clinical endpoint is achieved or until there is a decline in hearing. No consensus has been reached so far on the overall dosage, dosing methods, timing of delivery, treatment duration, clinical endpoint of therapy, or concentration of gentamicin. Both clinical evidence and basic science models should be further studied to scientifically elicit the most effective and safe regimen.

3. Mechanism of action

Aminoglycoside antibiotics have a well-documented history of cochleotoxic and vestibulotoxic effects. Administration of intratympanic aminoglycoside antibiotics to patients with MD is based on the notion that the patient's vestibular symptoms are due to the damaged and distorted vestibular signals emanating from their ear and that they are better off with no signal than with a damaged and distorted signal. The objective of ITG is to weaken vestibular signals in the Ménière's ear to the point at which they are no longer strong enough to generate a vertigo attack. Ideally, aminoglycosides would act to reduce vestibular function, and thus alleviate the patient's symptoms of vertigo, while preserving hearing. The degree to which a drug is cochleotoxic or vestibulotoxic differs among aminoglycosides. Gentamicin and streptomycin, for instance, are reported to be more vestibulotoxic. Other aminoglycosides, such as amikacin, are considered to be relatively more cochleotoxic and thus are not used transtympanically. The best evidence for this is the simple clinical observation that patients undergoing systemic gentamicin or streptomycin therapy experience vestibulopathy much more commonly than hearing loss. This feature has been used by otologists to control the vestibular symptoms of MD, initially provided through systemic delivery by Fowler [1] and subsequently through IT injections by Schuknecht [2, 8]. Use of streptomycin has been largely replaced by gentamicin which is thought to be more selectively vestibulotoxic and better able to preserve residual hearing in patients with unilateral MD refractory to medical management [9, 10].

Within the bony labyrinth, several studies have investigated the trafficking and distribution of aminoglycosides, finding different patterns of distribution dependent upon the dose, duration, and route of administration. IT-injected aminoglycosides appear to gain access to the inner ear via the oval window and the round window [11, 12], and uptake either by passive diffusion or by endocytosis [13, 14]. Salt et al. recently quantified diffusion of gentamicin through the oval (35%)

versus the round window (57%) [12, 15]. Access to these membranous structures is however uncertain, partly due to their variable permeability in individuals, resulting in unpredictable drug exposure of the inner ear [16–18]. Similar mechanisms of cellular trafficking (active diffusion and endocytosis) have been proposed in the transport of aminoglycosides into cells of the inner ear [19].

Once the drug crosses the oval window and the round window, the situation becomes more complex and the precise mechanism by which aminoglycosides exert their toxic effects on hair cells is unknown, to date. Previous animal studies showed that in the cochlea, sensory hair cells, the spiral ligament including the stria vascularis, and spiral ganglion cells had a very early uptake of gentamicin. Similarly, hair cells, dark cells, and vestibular ganglion cells are the primary targets in the vestibular system. This may demonstrate that gentamicin most likely diffuses across the inner ear membranes, readily achieving concentrations within the scala vestibuli, cochlear duct, and vestibule and then exerts its cellular toxicity.

Multiple mechanisms, including disruption of calcium-dependent cytokine production resulting in the damage to hair cell membrane integrity, increased superoxide production, hair cell transduction blockage, glutamate decarboxylase inhibition, ornithine decarboxylase inhibition, and free radical damage, all have been developed to explain aminoglycosides' direct toxicity to hair cells [10, 20, 21]. While most cells of the inner ear demonstrate aminoglycoside penetration, several studies have identified preferential loss of the hair cells at the basal turn of the cochlea over the apical hair cells and vestibular type I hair cells over their type II counterparts [22–26]. Direct damage to the spiral ganglion has also been observed [27] and histologic studies in rhesus monkeys suggest relative sparing of the maculae [28].

In parallel to previous findings, several studies have demonstrated that direct application of gentamicin into the vestibular labyrinth also causes greater loss of type I versus type II vestibular hair cells [29, 30]. Recently, Lyford-Pike et al. [26] used the animal model, chinchilla, to provide the evidence that the selective loss of type I hair cells assuredly occurred because these cells preferentially accumulate gentamicin acutely after intratympanic administration. Type II hair cells and supporting cells concentrate substantially less gentamicin. These results might theoretically ameliorate the more profound symptom of vertigo (driven by type I hair cells) while preserving cochlear function.

Aminoglycosides may also act to inhibit production of endolymph, restoring the balance between endolymphatic and perilymphatic pressure. This would also act to alleviate all symptoms of endolymphatic hydrops. Additionally, aminoglycosides are theorized to cause selective damage to the cells of the cochlear stria vascularis and planum semilunatum in the cristae ampullae of the semicircular canals, which are involved in ionic regulation and endolymph production [31]. It is also known that gentamicin utilizes the cellular machinery of endolymph production to traffic into the inner ear after systemic administration [32]. The theory that vestibular dark cells and, thus, endolymphatic flow, are the targets by which aminoglycosides alleviate vertigo is of significant clinical interest because it suggests that it is not necessarily important to ablate the vestibule to achieve vertigo control in MD. This idea can explain why patients with intact caloric responses can still achieve significant vertigo control after intratympanic aminoglycoside administration.

In conclusion, direct toxicity to vestibular hair cells and direct toxicity to the endolymph producing apparatus might be the two major mechanisms of action by ITG. Most importantly, gentamicin has been proved to be more vestibulotoxic than cochleotoxic in humans. The inner ear toxicity of gentamicin might follow an order. Secretory dark cells of the vestibule might be the first to be damaged, followed by

the vestibular neuroepithelium and the afferent vestibular fibers, and finally, the hair cells of the organ of Corti are destroyed [33, 34].

4. Therapeutic method and treatment efficacy

Ménière's disease is manifested by episodic vertigo, tinnitus, aural fullness, and fluctuating hearing loss. The treatment of patients with MD is usually directed at the most disabling symptom, which is the debilitating vertigo. MD treatment protocols typically measure vertigo control according to AAO-HNS Committee on Hearing and Equilibrium guidelines for grading vertigo severity [35]. Often, clinical trials also attempt to assess other disease sequelae such as hearing loss, tinnitus, and aural fullness.

As a well-known relapsing-remitting disease, it is rather difficult to accurately evaluate the efficacy of ITG in treatment of MD. Firstly, the natural history of remission and exacerbation of symptoms make evaluation of the effectiveness of treatment remarkably difficult. Commonly, vertigo attacks can improve without treatment of any kind as periods of remission are not uncommon. Thus, a clinical trial without controls will not account for this finding. Another difficulty is that clinical researchers attempt to show hearing preservation with IT gentamicin protocol, but hearing tends to worsen over time in MD regardless of treatment. Finally, the variable nature of MD with fluctuation in levels of hearing and even frequency and severity of vertigo can make clinical trials difficult.

To date, there have only been a few interventional randomized controlled trials investigating the true efficacy of ITG in the treatment of MD. In 2004, the first prospective, double-blind, randomized clinical trial of intratympanic gentamicin versus intratympanic buffer solution (placebo) in patients with active MD was reported by Stokroos et al. [36]. They performed ITG injections with buffered gentamicin (30 mg/ml) every 6 weeks until the vertigo complaints disappeared (12 patients received gentamicin versus 10 for placebo), outcome measures included the number of vertiginous spells, degree of sensorineural hearing loss, labyrinthine function, and labyrinthine asymmetry. Compared to the placebo group, topical gentamicin provided a significant improvement in the number of vertiginous attacks per year at follow up which varied between 6 and 28 months. There was no statistically significant change in hearing or other outcomes in two groups. However, hearing had a tendency to deteriorate in the placebo-treated patients, due to the natural course of the disease, which suggests that early treatment with topical gentamicin may preserve residual sensorineural hearing in active MD.

In 2008, Postema et al. [37] reported another prospective, double-blind, randomized, placebo-controlled trial associated with ITG therapy for control of vertigo in unilateral MD. They used weekly injections of 0.4 ml of gentamicin (30 mg/ml). A total of 4 injections were given through a ventilation tube (16 patients received gentamicin and 12 received a placebo). The results showed that gentamicin treatment resulted in a significant reduction of the score for vertigo complaints (including vertigo severity) and the score for perceived aural fullness. They also noted that a small increase in hearing loss (average of losses at 0.5, 1, 2, and 4 kHz: 8 dB HL) was measured in the gentamicin group.

In 2016, Patel et al. [38] performed a randomized, double-blind, comparative effectiveness trial of intratympanic methylprednisolone (n = 30) versus gentamicin (n = 30) in patients with refractory unilateral MD. Patients were randomly assigned (1:1) to two intratympanic methylprednisolone (62.5 mg/ml) or gentamicin (40 mg/ml) injections given 2 weeks apart, and were followed up for 2 years. In the methylprednisolone group, complete vertigo control (Class A) was achieved in 21/30 patients

(70%) compared to 25/30 (83.3%) in the gentamicin group. After methylprednisolone, 22 patients (78.5%) experienced an improved functional level score and 8 patients (28.7%) better pure-tone hearing and speech discrimination. There were also reductions for tinnitus, dizziness, and aural fullness. Fifteen patients (50%) required further courses of methylprednisolone. Two patients were deemed treatment failures and were assigned ITG treatment. The study showed no significant difference between the methylprednisolone and gentamicin for the control of vertigo, total number of injections, number of patients with relapsing vertigo, or the amount of pain from injection but better speech discrimination after methylprednisolone.

Based on the above prospective, double-blind, randomized controlled clinical trials, intratympanic gentamicin, as a medically ablative method, seems to be the most effective non-surgical treatment to eradicate vertigo in intractable MD, but with a potential risk of hearing loss. However, there is no consensus on the treatment protocol of ITG, especially for the concentration of gentamicin, dosage in each application, number of injection, and the time interval between two doses.

In the over 40 years of clinical trials in the treatment of MD by ITG, the majority are case series without controls, mainly because of the significant difficulties in conducting the randomized controlled clinical trials or case/control trials [33]. In earlier studies, the highest rate of vertigo control was reported with daily injections or multiple titrations. On the other hand, considerable hearing loss was experienced in several studies. Moller et al. [39] treated 15 patients with disabling MD with daily injections for periods ranging from 3 to 11 days. They achieved 93.4% of vertigo control, but also 33.4% of hearing loss. They reported that none of the patients were responsive to caloric stimulation. Laitakari [40] reported 90% of vertigo control and 45% of hearing loss in 20 patients who had daily ITG for a minimum of 3 consecutive days. Parnes and Riddell [41] reported 41.7% worsening of the hearing in their group of patients who received three daily injections within 4 days. Murofushi et al. [42], using several daily injections, reported hearing loss in 30% of cases. Corsten et al. [43] reported 81% vertigo control but 57% hearing loss in patients (n = 21) who had gentamicin instillation 3 times a day for 4 consecutive days. Kaplan et al. [44] reviewed the 10-year long-term results of 114 patients treated with gentamicin instillation 3 times a day for 4 consecutive days. They achieved 93.4% of vertigo control and 25.6% of hearing loss.

In the early 2000s, regarding patients with hearing deterioration and even those becoming deaf, there was a discussion about reducing the gentamicin dose or performing the application at longer intervals. Daily titration methods were abandoned. Transtympanic gentamicin therapy was modified to weekly or monthly intervals as "needed" or "on demand" to reduce the symptoms of MD, aiming to maintain cochlear as well as vestibular function. Harner et al. [45] reported a very high rate of vertigo control with preservation of hearing in 43 patients. There were no patients with changes in cochlear function and ablation of the labyrinth. All patients received one injection, and half of them received a repeat injection 1 month after therapy. Minor [46] used gentamicin on weekly intervals until the development of spontaneous nystagmus, head-shaking nystagmus, or head thrust sign. Vertigo was controlled in 91% of the patients, and profound hearing loss only occurred in 1 patient. Atlas and Parnes [47] reviewed the outcomes of 83 patients who received weekly injections. They reported hearing loss in 17% of the patients, with vertigo control in 84%. Martin and Perez [48] reported vertigo control in 83.1% of the patients and hearing loss in 15.5% of them after gentamicin at weekly intervals. De Beer et al. [49] reported 15.8% with hearing loss and 80.7% with vertigo control after, between 1 and 10, intratympanic injections at a minimum interval of 27 days. Casani et al. [50] reported 12% hearing loss after a maximum of 2 injections of gentamicin and 81% vertigo control.

Most recently, Vlastarakos et al. [51] published a systematic review looking at sustained-release delivery of IT gentamicin (dynamic-release versus sustained-release vehicles). Dynamic release (microcatheter at the round window) was found to provide satisfactory vertigo control in 89.3% (70.9% reporting complete control). Sustained-release preparations (gentamicin-soaked wick/pledget) provided 82.2% satisfactory control in the pool of patients (75% with complete control). In patients receiving sustained-release preparations, complete hearing loss was reported in 31.1% patients with another 23.3% of patients experiencing partial hearing loss. This adverse change in hearing was unacceptably high, reinforcing the suggestion of using a sustained-release vehicle only in patients who had failed IT gentamicin injections previously or those without serviceable hearing.

Commonly, intratympanic injection under otoscope or microscope is a simple and recommendable technique. The desired amount of gentamicin is injected over the round window through the posterosuperior quadrant of the tympanic membrane. There are two common doses of gentamicin for injection. The standard intravenous preparation of gentamicin is 40 mg/ml, which can be buffered with 8.4% sodium bicarbonate so that discomfort on injection is reduced. A total of 1.5 ml of gentamicin mixed with 0.5 ml of sodium bicarbonate at these concentrations will produce a final concentration of 26.6 mg/ml gentamicin. Approximately 0.3–0.5 ml of solution is usually adequate to bathe the round window in solution. Typically, patients will remain lying flat with the injected ear up for 10 min to 1 h. This procedure is generally well tolerated by patients, who should be told to expect brief pain on injection, followed by possible vertigo or disequilibrium. Warming the medication can help in this regard (preventing a cold caloric response).

Based on the combination of current clinical practice, basic science models, and results from clinical trials, low drug dose and long interval between injections, mainly in order to reduce the risk of deafness, are reasonably encouraged. The low dose method involves using 1–2 injections of gentamicin and waiting a month or 2 weeks between injections. The rate of vertigo control may be up to 80–90%, with no significant side effects. The second injection is given only if there has been a vertigo spell 2 weeks prior. In other words, instead of titrating to the onset of damage to the vestibular system, the criterion is a positive effect on the disease. Occasionally, a third dose is given.

In short, whatever technique is used, the goal is to apply gentamicin to the round window in sufficient concentration and over a sufficient amount of time that it achieves a therapeutic effect while avoiding both local and systemic side effects, especially hearing loss.

5. Indications and contraindications

Not all patients with MD can be treated with ITG. Based on the international consensus on treatment of MD obtained from the IFOS meeting 2017 [52], MD should be treated with a step-by-step therapy. The first line of treatment includes the medical conservative treatment, such as dietary modification and oral medicine. After this line of treatment, 80% of patients with MD are cured or in remission. When the vertigo of MD fails to be controlled by the first-line treatment for more than 6 months, it will be regarded as intractable MD. Then the second line is the IT injections, mainly IT steroids as a conservative treatment and ITG in the case of IT steroid failure, and preferentially in patients with hearing impairment. After the second line treatment, 90–95% of the total

patients are cured or in remission. The third line is the surgical, either conservative or destructive, treatment. For unilateral intractable MD with serviceable hearing (i.e., speech reception threshold better than 50 dB HL and speech discrimination score of more than 50%) in the treated ear, treatment protocol with an injection repetition not shorter than 1 week between adjacent injections or one with injections on a monthly basis as “needed” is preferred. These methods provide the same level of vertigo control yet offer better preservation of hearing functions [33].

The best indication for ITG treatment appears to be the control of vertigo in profound hearing loss or non-serviceable ears, in which speech reception threshold is worse than 50 dB HL and speech discrimination score less than 50% [53, 54]. Under these scenarios, there is no need to consider the risk of deafness, and titration methods or multiple injections on a daily basis are preferred, since these methods have significantly elevated incidence of hearing loss [33]. Transmastoid labyrinthectomy has traditionally been offered for non-serviceable ears in patients with MD. This method has been the gold standard, and it is very effective in eradication of vertigo in more than 94% of patients. In comparison, ITG therapy provides a minimally invasive ambulatory substitute with low morbidity and fewer side-effects, which is also very cost effective to manage vertigo in these MD patients with non-serviceable ears [53].

Another important indicator is the control of vertigo in patients who have failed endolymphatic sac surgery. Marzo and Leonetti [55] have shown the effectiveness of ITG therapy for patients who have failed endolymphatic sac surgery, thus reducing the need for vestibular neurectomy in those with intractable disease.

To be allergic and hypersensitive to aminoglycosides are two absolute contraindications for ITG. It is worth noting that patients who carried the mitochondrial mutation of the gene MT-RNR1 (mitochondrially encoded 12S ribosomal RNA) are hypersensitive to aminoglycosides. A single injection of aminoglycosides results in complete and definitive deafness in subjects with this mutation [56]. A systematic genetic screening of MD patients is highly recommended to prevent the occurrence of bilateral deafness. The treatment is intended for the abolition of vestibular function; thus, administration of gentamicin must be done carefully in the elderly, who have difficulty attaining vestibular compensation, in patients with complications, or in those with bilateral MD. Taking also into consideration the fact that individual's drug sensitivity depends on their genetic background, investigation of appropriate drug levels according to evidence-based medicine remains a future task.

6. Complications

The complications of ITG treatment are primarily bi-fold: one is the risk caused by drug toxicity of gentamicin, the other is the risk caused by intratympanic injection. Undoubtedly, the main risk of ITG treatment for vertigo is the sensorineural hearing loss and associated prolonged disequilibrium and ataxia, which are common complaints after this treatment. Less common side effects include local hemorrhage, allergic response and tympanic membrane perforation (especially in an irradiated or otherwise damaged tympanic membrane), local discomfort, inflammation, otitis media or externa, and transient vertigo caused by a caloric reflex effect from the instilled fluid [38, 57]. It is also critical to educate all patients who are given intratympanic aminoglycosides that bilateral permanent hearing loss is possible, even from one single unilateral injection.

7. Conclusions

Intratympanic injection of gentamicin is probably the most effective non-surgical treatment to eradicate vertigo in MD. But it is also an ablative method that carries a non-negligible risk of hearing loss. Gentamicin has been proved to be more vestibulotoxic than cochleotoxic; direct toxicity to vestibular hair cells and direct toxicity to the endolymph producing apparatus might be the two major mechanisms of action. To date, no consensus has been reached on the dosage, dosing methods, timing of delivery, treatment duration, clinical endpoint of therapy, and concentration of gentamicin. However, based on the combination of current clinical practice, basic science models, and results from clinical trials, low drug dose and long intervals between injections are reasonably recommended. The application of gentamicin-induced vestibular ablation has minimized the number of more invasive procedures such as unilateral labyrinthectomy and vestibular neurectomy. In comparison with surgery, the vertigo control is comparable, the overall cost is reduced, and complications are limited. ITG in treating intractable MD has gradually become a prevalent therapy during the past decades. However, to administer ITG treatment, multiple factors should be comprehensively considered including patient selection, pharmacological mechanism, drug dose, the interval of administration, complications, indications, and contraindications.

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The authors declare no competing financial interest.

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