CASE REPORT

Irreversible Atorvastatin-Associated Hearing Loss

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Drug-associated ototoxicity is a potentially irreversible adverse event. Among the several 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) available in the United States, only atorvastatin is associated with tinnitus, but none are associated with any forms of hearing loss. A search of the published literature (1950–August 2011) revealed no published case reports of ototoxicity associated with statins. To our knowledge, we describe the first case of progressive, irreversible hearing loss in a 32-year-old man 18 months after starting atorvastatin therapy. He began taking atorvastatin 20 mg every evening for treatment of hypercholesterolemia. Six months later, he complained of occasional episodes of tinnitus, which resolved spontaneously. An audiogram was obtained and was normal. By 18 months, the tinnitus became continuous. Another audiogram revealed bilateral "cookie-bite" middle-frequency hearing loss. Atorvastatin was immediately discontinued, and the patient was fitted with hearing aids. Four years after drug discontinuation, his hearing loss had neither progressed nor regressed. Use of the Naranjo adverse drug reaction probability scale indicated a possible (score of 2) temporal and causal relationship between the patient's hearing loss and atorvastatin. Causes of "cookie-bite" hearing loss include chronic exposure to loud noises, presbycusis, genetic predisposition, and drugs. The manufacturer of atorvastatin has received three unpublished cases of deafness, but claims that causal relationships were not established. Despite these claims by the manufacturer, based on this case report, we recommend that clinicians and patients be aware of the risk of atorvastatin-associated tinnitus and permanent hearing loss. Further research is needed to better understand the mechanism and frequency of this adverse event.

Key Words: atorvastatin, hearing loss, ototoxicity, tinnitus, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, statins, adverse drug event.

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The discovery of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) has revolutionized the treatment of hypercholesterolemia and hyperlipidemia. The Framingham Heart Study showed that elevated serum low-density lipoprotein cholesterol (LDL) levels are a major risk factor for coronary heart disease events. As a result, the National Cholesterol Education Program Adult Treatment Panel III recommends statins for both primary and secondary prevention of coronary heart disease.[1]

Postmarketing surveillance of statins, however, revealed significant adverse drug events including fatal cases of rhabdomyolysis, which led to the market withdrawal of cerivastatin in 2001.[2] Of all the currently available statins in the United States, only atorvastatin is associated with tinnitus or perception of ringing in the ear.[3–8] None of the statins have been associated with any forms of hearing loss.[3–8] For any drug, episodes of tinnitus may go unnoticed or ignored by the patient, which may progress to permanent hearing loss if

the causative agent is not discontinued early.[9] As of 2010, atorvastatin is the second top-selling drug in the United States.[10] The five most commonly reported adverse drug events for atorvastatin are arthralgia, diarrhea, nasopharyngitis, pain in extremity, and urinary tract infection.[3]

We describe a patient who developed progressive, irreversible hearing loss 18 months after atorvastatin therapy was started for the treatment of hypercholesterolemia.

Case Report

A 32-year-old Caucasian male pharmacist and a medical science liaison was prescribed oral atorvastatin 20 mg every evening for the management of hypercholesterolemia secondary to long-term use of prednisone for Crohn's disease. His family history was significant for hypercholesterolemia, hypertension, coronary heart disease, and type 2 diabetes mellitus. He denied significant trauma to the ears or persistent occupational or recreational exposure to loud noises. With the exception of chronic allergic rhinitis (time of diagnosis unknown), the patient had no known history of allergies, hearing loss, ear infections, or obesity. It was not known if the patient's rhinitis was adequately controlled while taking atorvastatin. In addition, he denied smoking and had no known significant history of drinking grapefruit juice or wine. In addition to Crohn's disease for 19 years, his medical history was significant for strictureplasty and small-bowel resection of the terminal ileum 18 years earlier, strictureplasty of small bowel 6 years earlier, and cadaveric right anterior cruciate ligament replacement 2 years earlier. His 10-year Framingham risk score was less than 1%.

Before starting atorvastatin, the patient's drug therapy consisted of oral budesonide 12 mg/day for maintenance of remission of Crohn's disease, oral cetirizine 5 mg–pseudoephedrine 120 mg/day as needed for allergic rhinitis, diphenoxylate 2.5–5 mg/atropine 0.025–0.050 mg orally as needed for diarrhea, oral famotidine 40 mg twice/day, and oral hyoscyamine 0.125–0.250 mg 3 times/day as needed for gastrointestinal spasms. Furthermore, the following drugs were used as needed for flare-ups of Crohn's disease: oral prednisone 5–60 mg/day, oral moxifloxacin 400 mg/day, and oral metronidazole 500 mg 3 times/day. Budesonide inhaler 2 puffs/day to each nostril for chronic allergic rhinitis and oral valsartan 160 mg –hydrochlorothiazide 12.5 mg once/day were added on months 6 and 12 of atorvastatin therapy, respectively. No 5-aminosalicyclic acid (5-ASA) derivative was prescribed while the patient was taking atorvastatin, although it was not clear if the patient ever received any 5-ASA agent for Crohn's disease. Besides the addition of budesonide inhaler and valsartan-hydrochlorothiazide, no other drugs were added, removed, or changed during the course of atorvastatin therapy. The patient denied taking any alternative medicine or over-the-counter agents, or receiving any vaccines.

Alanine aminotransferase, aspartate aminotransferase, serum albumin, albumin:globulin ratio, total bilirubin, alkaline phosphatase, and blood urea nitrogen levels were within normal limits during the patient's atorvastatin use (Table 1). In addition, high-density lipoprotein cholesterol (HDL), LDL, triglyceride, and total cholesterol levels were assessed for adherence to atorvastatin. The patient did not take any other drugs known to affect these markers besides prednisone.

Six months after starting atorvastatin, the patient noticed spontaneous episodes of tinnitus in both ears several times a week, with each episode lasting 5–10 minutes. He subsequently visited an otolaryngologist to assess the tinnitus. An audiometry test involving the assessment of both air and bone conduction thresholds for pure tones between 250 and 8000 Hz was performed. An audiologist interpreted the audiogram findings from the test as unremarkable. Figure 1 depicts a sample of an audiogram representing normal hearing (the patient's original audiogram could not be retrieved from storage by the patient's otolaryngologist). During this visit, the otolaryngologist prescribed budesonide inhaler 2 puffs/day to each nostril for chronic allergic rhinitis.

At month 12 of atorvastatin therapy, oral valsartan 160 mg–hydrochlorothiazide 12.5 mg once/day was prescribed for hypertension. From months 6–18, the frequency of tinnitus increased until it became continuous. A visit to the otolaryngologist was also prompted on month 18 by

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the patient's inability to hear his child's high-pitched cries. An audiogram reading was immediately obtained and confirmed that the patient had developed bilateral "cookie-bite" middle-frequency hearing loss likely from an exogenous source (Figure 2). Atorvastatin was immediately discontinued, and the patient was fitted with hearing aids in both ears. No change was made to the patient's drug regimen for Crohn's disease before or after discontinuation of atorvastatin.

At month 23 after starting atorvastatin therapy (5 mo after discontinuing the drug), the patient's hearing threshold did not worsen or improve (Figure 3). As an immediate alternative for the management of hypercholesterolemia, the patient's primary care provider recommended the Atkins nutritional approach with physical exercise for about 2 years before prescribing oral ezetimibe 10 mg–simvastatin 20 mg every evening. It was not known if the patient was adherent to the recommended dietary plan. Approximately 4 years after starting atorvastatin (30 mo after discontinuing the drug) and 6 months after ezetimibe-simvastatin was initially prescribed, the patient's severe hearing loss had neither progressed nor regressed (Figure 4).

Discussion

Types of Hearing Loss

There are three types of hearing loss: conductive, sensorineural, and mixed, which is a combination of both conductive and sensorineural hearing losses.[11] Conductive hearing loss is defined as decreased sound conduction in the outer and/or middle ear; it can be caused by acute or chronic otitis media, and impacted earwax. Sensorineural hearing loss, however, is characterized by damage to the auditory nerves located in the inner ear, and unlike conductive hearing loss, it is generally irreversible. Aging, exposure to intense environmental noises, viral infections, and ototoxic drugs (e.g., aminoglycoside antibiotics, loop diuretics, salicylates, and platinum-based chemotherapeutic agents) are primarily responsible for the sensorineural type of hearing loss.[11] Cookie-bite hearing loss is one of the five most recognized patterns of sensori-

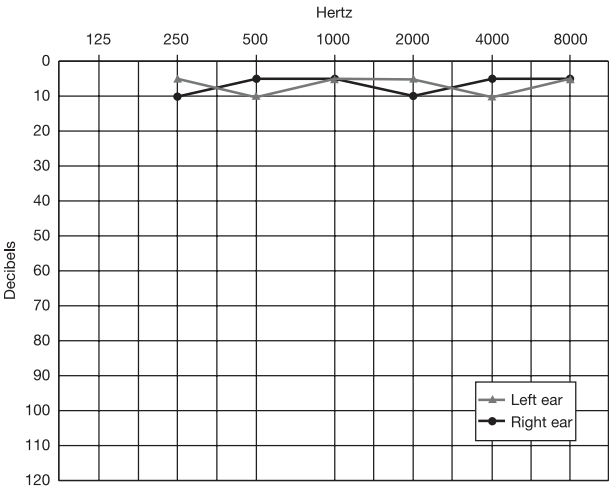

Figure 1. Sample audiogram representing normal hearing. On the horizontal axis is the frequency or pitch going from low (250–1000 Hz), to middle (1000–4000 Hz), to high (4000–8000 Hz) frequencies. The vertical axis represents intensity or loudness going from low to high (0–120 decibels). Any decibel of 16 or higher indicates hearing loss and worsening of hearing threshold (ability to detect the sound) within the corresponding frequency. The higher the value, the more severe the loss.

Table 1. Pertinent Laboratory Values During Atorvastatin Therapy

	Time After Atorvastatin Was Started					
Laboratory Test	0	3 mo	7 mo	11 mo	12 mo	18 mo
Aspartate aminotransferase (U/L)	31	16	19	24	24	12
Alanine aminotransferase (U/L)	47	26	30	39	28	8
Alkaline phosphatase (U/L)	58	53	49	61	55	77
Total bilirubin (mg/dl)	0.4	0.3	0.43	0.29	0.33	0.3
Total protein (g/dl)	7.4	6.5	6.1	6.8	6.4	5.6
Albumin:globulin ratio	1.5	1.5	1.7	1.5	1.4	1.5
Triglyceride level (mg/dl)	NT	284[a]	156[a]	NT	191[a]	274[a]
Cholesterol levels (mg/dl)						
Total cholesterol	NT	213[a]	180	NT	208[a]	221[a]
High-density lipoprotein	NT	46[a]	56[a]	NT	36[a]	36[a]
Low-density lipoprotein	NT	110[a]	93	NT	134[a]	130[a]
Blood urea nitrogen (mg/dl)	NT	13	19	NT	11	10

NT = not tested.

Normal ranges are as follows: aspartate aminotransferase 2–50 U/L; alanine aminotransferase 2–60 U/L; alkaline phosphatase 20–125 U/L; total bilirubin 0.2–1.5 mg/dl; total protein 6.0–8.3 g/dl; albumin:globulin ratio (calculated) 0.8–2.0; triglyceride <150 mg/dl; total cholesterol <200 mg/dl; high-density lipoprotein cholesterol >59 mg/dl; low-density lipoprotein cholesterol <100 mg/dl; blood urea nitrogen 7–25 mg/dl.

[a]Abnormal value.

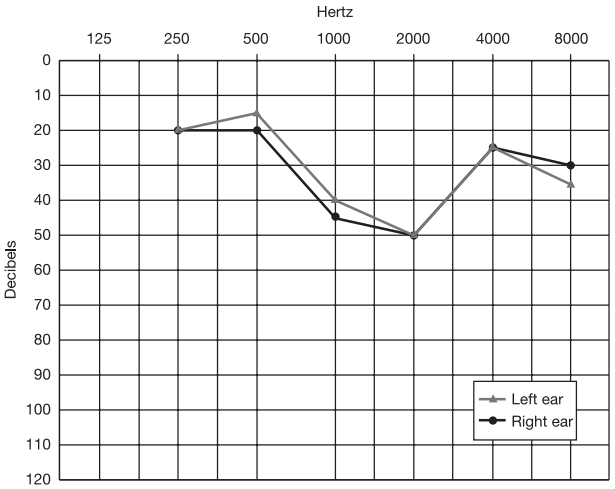

Figure 2. The patient's audiogram obtained at month 18 after starting atorvastatin therapy. The hearing thresholds for both ears have significantly increased in the middle frequency (up to 50 decibels) and slightly increased in the high frequency (up to 35 decibels), but remained relatively normal in the low frequency. This represents bilateral middle-frequency, or "cookie-bite," hearing loss.

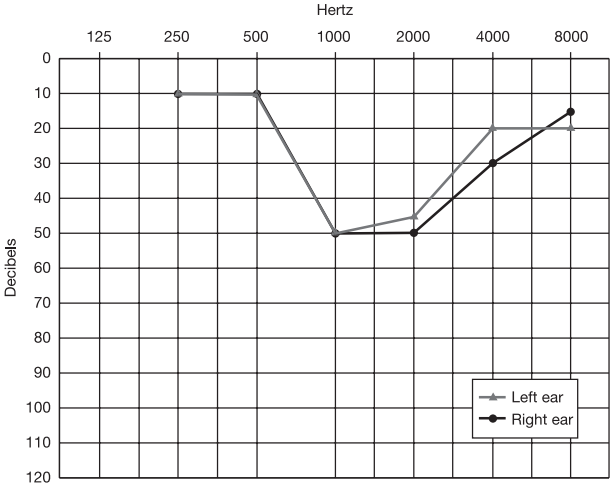

Figure 3. The patient's audiogram obtained at month 23 after starting atorvastatin therapy (5 mo after discontinuing the drug). Compared with Figure 2, the hearing thresholds for both ears have remained relatively the same for all frequencies.

neural hearing loss and is characterized by dip (s) in the middle frequencies of an audiogram,[12] as shown in Figure 2 for our patient. Patients are at an increased risk for developing cookie-bite hearing loss if they have a known family history of hearing loss or if they receive a diagnosis of vestibular schwannomas, although cookie-bite hearing loss may manifest spontaneously.[13] Among the conditions in the patient's medical history, only hyperlipidemia is associated with hearing loss.[14]

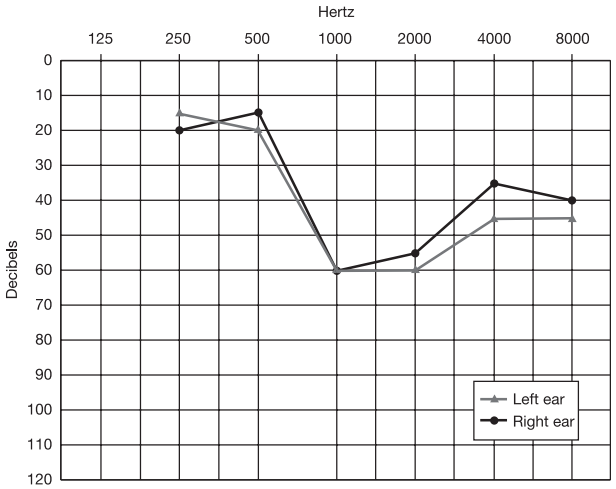

Figure 4. The patent's audiogram obtained at month 48 after starting atorvastatin therapy (30 mo after discontinuing the drug). The hearing thresholds for both ears continue to slowly increase in the middle frequency (up to 60 decibels). They also increased for the high frequency (up to 45 decibels), but remained relatively normal for the low frequency. At this time, the patient had been taking ezetimibe-simvastatin for 6 months. The bilateral middle-frequency, or cookie-bite, hearing loss is permanent.

Review of the Case and Literature Search

Our patient developed irreversible, middle-frequency bilateral hearing loss 18 months after starting atorvastatin therapy. Episodes of tinnitus were first noted by the patient 6 months after atorvastatin was started. Application of the Naranjo adverse drug reaction probability scale yielded a score of 2, indicating a possible temporal and causal relationship between atorvastatin and hearing loss.[15]

No other drugs were added during the course of atorvastatin therapy besides a budesonide inhaler and valsartan-hydrochlorothiazide. No significant drug-drug interaction was noted among his drug therapies. Budesonide was started 6 months after atorvastatin was started, and it is associated with unspecified ear infections, with a prevalence of less than 5%.[16] However, the patient reported no history of ear infections. Valsartan-hydrochlorothiazide, on the other hand, is associated with a greater than 0.2% prevalence of tinnitus but not hearing loss, according to the drug's prescribing information.[17] Nevertheless, the combination drug was started 12 months after atorvastatin was pre-

scribed and 6 months after tinnitus had already begun.

Atorvastatin and its metabolites are extensively metabolized by the cytochrome P450 (CYP) 3A4 isoenzyme and primarily eliminated through the biliary route.[3] However, angiotensin II receptor blockers such as valsartan minimize the hypertensive effects mediated by angiotensin II.[17] Enzymes responsible for the metabolism of valsartan have not been identified but are suspected not to involve the CYP isoenzymes.[17] Valsartan is not a known inhibitor or inducer of any drugs.[17] Hydrochlorothiazide is not metabolized but eliminated through renal excretion. Because of pharmacodynamic and pharmacokinetic differences, no drug interactions are expected between atorvastatin and either valsartan or hydrochlorothiazide. Based on these findings, the combination drug most likely had not played an additive or synergistic role to the tinnitus produced by atorvastatin.

Other concurrent drugs taken by the patient that are associated with tinnitus include famotidine and moxifloxacin, with prevalence of undefined and less than 0.1%, respectively.[18, 19] Nevertheless, both were started years before atorvastatin was started, and hearing loss and tinnitus had not occurred. No other drugs that the patient was taking have been associated with any types of auditory dysfunction, hearing loss, or symptoms of hearing loss.[20–25]

With regard to laboratory parameters, total cholesterol, LDL, and triglyceride levels decreased and HDL levels increased from months 3–7 (Table 1), which suggest adherence to atorvastatin therapy. However, between months 12 and 18, the opposite occurred for all parameters. The patient reported that between months 15 and 18, prescriptions for atorvastatin were not provided by his primary care provider. Instead, he took samples of atorvastatin 20 mg at his own discretion, with unknown dosing frequency. Also during this time period, he experienced spontaneous flare-up episodes of his Crohn's disease, which were alleviated with prednisone doses up to 60 mg/day. The mean duration of flare-up episodes is unknown. Inconsistent use of atorvastatin coupled with high doses of prednisone most likely caused the significant rise in LDL, triglyceride, and total cholesterol levels and decrease in HDL level at month 18. No laboratory tests were available at months 6 and 48.

As mentioned, hyperlipidemia is associated with the development of hearing loss. The exact pathophysiologic mechanism is unknown, but proposed mechanisms are multifactorial including increase blood viscosity of the cochlear vessels resulting in decreased oxygen transportation to the cochlea, and increase production of reactive oxygen species.[14, 26] The prevalence of hyperlipidemia and the severity of tinnitus were assessed among patients with long-term exposure to noises who had high-frequency hearing loss confirmed by a pure tone audiometry test.[14] Patients excluded were those who had a medical history of familial hearing loss, chronic otitis media, collagen disease, or neurologic or hormonal disturbance, as well as exposure to ototoxic drugs. Of the 120 patients assessed, 42 (35%) had hypercholesterolemia or hypertriglyceridemia, or both. Unfortunately, the study had significant limitations, including no numeric definitions for both hypercholesterolemia and hypertriglyceridemia, whether statins were prescribed before enrollment, whether hearing loss may have been caused solely by chronic noise exposure, and the possibility of age-related hearing loss or presbycusis.

The prevalence of hyperlipidemia among human subjects with sensorineural hearing loss ranged significantly among different studies, from 5–38%.[26, 27] In addition, in one of the studies, the authors found no difference in hearing level between men and women aged 40–59 years in the high-level group (serum lipid concentration ≥ 1 SD from the mean) and low-level group (serum lipid concentration ≤ 1 SD from the mean).[26] The mean total cholesterol levels for the men and women were 202.9 ± 32.5 and 210.9 ± 39.1 mg/dl, respectively. The mean total triglyceride levels were 139.7 ± 78.4 and 81.5 ± 46 mg/dl for the men and women, respectively.

Based on inconsistent findings among the studies,[14, 26, 27] coupled with the lack of persistent exposure to loud noises by our patient, it remains unclear whether the patient's uncontrolled lipid profile (Table 1) may have contributed to the hearing loss.

A comprehensive literature search was conducted on PreMEDLINE and MEDLINE from 1950–August 2011, and Clin-Alert. Search terms used include generic names of all marketed statins, HMG-CoA reductase, ototoxicity, tinnitus, hearing loss, vestibulocochlear nerve, auditory nerve, and acoustic nerve. No limits were applied. The search revealed no published literature on statin-associated ototoxicity. Instead, the search yielded two studies, one in humans[28] and one in mice,[29] that demonstrated atorvastatin as being beneficial rather than detrimental in hear-

ing loss. We also requested the International Drug Information Center (IDIC) of the Arnold and Marie Schwartz College of Pharmacy and Health Sciences of Long Island University to conduct a thorough literature search to determine whether ototoxicity has been associated with the use of statins. Databases searched by the IDIC included MEDLINE, Iowa Drug Information Service, International Pharmaceutical Abstracts, Physicians' Desk Reference, Lexi-Comp Online, Micromedex Healthcare Series, Clinical Pharmacology, the U.S. Food and Drug Administration Web site, and an Internet search with Google as the search engine. The search resulted in no reports.

A telephone conversation with the manufacturer of atorvastatin revealed three spontaneous reports of atorvastatin-associated ototoxicity (S. Schilit, Pfizer Inc., oral communication, 2007). However, according to the manufacturer, a causal relationship could not be established for the reports, and they are not accessible for personal review.

Available Studies on Atorvastatin and Hearing

As mentioned earlier, a literature search revealed two studies that concluded that atorvastatin improves hearing loss.[28,29] In the first study, the objective of the placebo-controlled trial was to determine whether statins slow down the progression of presbycusis in humans.[28] Patients aged 60–75 years with presbycusis and a baseline serum LDL level of 100–190 mg/dl and not treated with any statins were included. The treatment group (26 patients) received oral atorvastatin 40 mg/day for a total duration of 13 months, and another 24 patients received placebo. The primary outcome was mean deterioration in hearing thresholds at months 0, 7, and 13, with score from the tinnitus questionnaire as the secondary outcome. The tinnitus questionnaire is composed of 10 questions, and it assesses the effect of tinnitus on the person's emotional well-being, sleep patterns, interference with work and leisure, auditory perceptions, and general health.[30] The total score may range from 10–50, with higher scores indicating increased negative impact on those parameters by tinnitus.

The mean deterioration for both ears and across all frequencies was higher in the atorvastatin group compared with the placebo group (1.30 vs 1.07 decibels).[28] The investigators rationalized that the reason that the atorvastatin group experienced an overall higher mean deterioration in hearing threshold was due to a clinically "common phenomenon," in which the first audiogram usually yields a hearing threshold a few decibels lower than subsequent ones. No baseline values, trends, or statistical analysis for hearing thresholds were provided. Compared with baseline, subsequent tinnitus scores improved for the atorvastatin group whereas it worsened for the placebo group by month 13, although the difference was not statistically significant ($p=0.083$). After 7 and 13 months, total cholesterol and LDL levels were lower in the atorvastatin group ($p<0.001$).

It is important to note that the investigators did not support their claim for the "common phenomenon" with any reference. Even if such a phenomenon exists, it can be argued that it would also affect the placebo group, leading to a null effect. Another limitation of the study is the failure to exclude confounders that could have affected the results, such as previous or concurrent use of ototoxic drugs. Although not necessarily a limitation, the research grant for the study was provided by the manufacturer of atorvastatin.

In the other study, the goal was to investigate the effects of atorvastatin on hearing in two genetic species of aging mice: the C57BL/6J and apolipoprotein E knockout (apoE−/−) mice.[29] Of the two species, the apoE−/− mouse is genetically predisposed to progressive hearing loss secondary to atherogenic hypercholesterolemia. Each species had their own respective treatment and placebo groups (17 mice for each treatment and control groups of the C57BL/6J species, and eight mice for each treatment and control groups of the apoE−/− species). Treatment groups were given atorvastatin 10 mg/kg/day. The trial lasted for 2 months. The primary outcome was difference in distortion product otoacoustic emissions (DPAOE) within both respective treatment and placebo groups. The DPAOE measures the sensitivity of the cochlea to pure-tone sounds at specific frequencies.[31] The investigators also monitored total serum cholesterol level, as well as both intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Both molecules are markers of atherosclerotic-induced inflammation, and they were measured to determine whether atorvastatin's effects on hearing are due to its antiinflammatory properties. These markers were measured once at the end of the trial. Statistical significance was defined as a p value less than 0.05.

For DPOAE, statistical significance was detected at the higher frequency range in favor of the C57BL/6J treatment group compared with its placebo group, unlike the apoE−/− mice for which there was no statistically significant difference.[29] For cholesterol level, no statistically significant difference was detected between the C57BL/6J treatment and control groups, whereas the apoE−/− treatment group had higher total cholesterol levels than those of the control mice. For both ICAM-1 and VCAM-1, statistically significant decreases were noted for the C57BL/6J treatment group compared with its corresponding control group. No statistically significant differences in both markers were detected between the apoE−/− groups. Based on these findings, the investigators concluded that atorvastatin slows down the deterioration of inner-ear functions not by its cholesterol-lowering effects, but through its lipid-independent, antiinflammatory effects.

The mouse study did not use a randomization protocol, and the sample sizes for both species of mice were relatively small.[29] Because the subjects of the study were mice, further studies with a similar experimental design adjusted for humans are needed to investigate atorvastatin's ability to prevent the progression of hearing loss through its antiinflammatory effects. Results obtained from animal research do not always result in similar conclusions in humans.[32–34]

In the human study, atorvastatin lowered total cholesterol and LDL levels significantly, increased deterioration of hearing threshold, and decreased tinnitus score in patients aged 60–75 years, although differences between these outcomes and placebo or baseline were not statistically significant.[28] However, in the mouse study,[29] the drug did not lower cholesterol levels significantly, resulted in higher DPOAE levels or sensitivity to sounds at higher frequencies, and lowered inflammatory markers in C57BL/6J normolipidemic wild-type mice. The relief of tinnitus found in the human study was mediated by atorvastatin's cholesterol-lowering effects and/or through antiinflammatory effects.[28] In the other trial, enhanced sensitivity of the cochlea was only mediated through the drug's antiinflammatory effects.[29] Despite the different study designs, both studies reached the same conclusion: atorvastatin slows down the deterioration of hearing loss.[28, 29] In spite of this, we reject the outcomes found in the human study[28] because of major limitations such as previous and/or concurrent use of ototoxic drugs. As mentioned, a similar experimental design adjusted for humans is needed to determine if findings in the mouse study[29] are also present among humans.

Potential Mechanism of Atorvastatin-Related Ototoxicity

Based on results from our literature search and review of prescribing information of all currently marketed statins in the United States, tinnitus may be specific to atorvastatin.[3–8] Our patient was prescribed ezetimibe-simvastatin more than 2 years after atorvastatin was discontinued. Figure 2 represents the hearing threshold of the patient while receiving atorvastatin, and Figure 3 shows the threshold 5 months after atorvastatin was discontinued. Figure 4 shows the threshold 6 months into ezetimibe-simvastatin therapy. Comparison of Figures 2 and 3 with Figure 4 reveals that the hearing threshold neither significantly improved nor worsened; therefore, simvastatin did not have any effect on the hearing threshold for our patient.

Although the exact mechanism for atorvastatin to cause hearing loss is unknown, it may involve decreased efficiency of prestin, a motor protein essential for auditory processing. Prestin is located in the cochlea and functions by sensing voltage differences across the outer hair cell membrane.[35] The voltage differences produce a change in prestin's molecular confirmation, which is essential for outer hair cells' ability to amplify sounds. The activity of prestin peaks at a voltage of −60 millivolts. Changes in cholesterol at the outer hair cell membrane alter the local voltage and, therefore, may move prestin out of its operational voltage range resulting in a decline in hearing. The use of statins may decrease cholesterol level at the outer hair cell membrane; however, it remains unclear whether lowering of serum cholesterol levels translates to decreased cholesterol levels at the membrane.

Limitations

Our case report has three limitations. The patient's baseline audiogram reading was not available according to the patient's otolaryngologist. However, the patient did not experience tinnitus before starting atorvastatin therapy. In addition, since part of the information was based on the patient's own account, recall bias is possible. Nonetheless, the patient's description of the case coincided with laboratory data, audiogram readings, prescription profiles, and other medical

information provided. Finally, the patient had uncontrolled hyperlipidemia, a condition that is associated with hearing loss. As stated earlier, however, the clinical significance of the patient's hyperlipidemia on hearing loss is unclear. The patient did not have long-term exposure to a significant degree of environmental noises.

Conclusion

To our knowledge, we describe the first case of irreversible atorvastatin-associated tinnitus and sensorineural, middle-frequency hearing loss. Despite the manufacturer's claim that a causal relationship between atorvastatin and hearing loss has not been established, we recommend that both clinicians and patients be cognizant of the risk of tinnitus and hearing loss associated with atorvastatin. Further trials investigating the risk for this possible adverse event are warranted.

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