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Third generation bisphosphonates for treatment of sensorineural hearing loss in otosclerosis

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Abstract

Objectives/Hypothesis—Otosclerosis is a disease of abnormal bone remodeling in the otic capsule. Although several drugs that inhibit bone remodeling, including sodium fluoride and first generation bisphosphonates, have been tried, there remains no clearly effective treatment for otosclerosis-related sensorineural hearing loss (SNHL). Over the past several years, third generation bisphosphonates, with more powerful anti-resorptive properties and increased bone affinity, have been developed and have demonstrated effectiveness in the treatment of osteoporosis and other metabolic bone diseases. We hypothesized that newer generation bisphosphonates, such as risedronate and zoledronate, would be effective in slowing the progression of SNHL in patients with otosclerosis.

Study design—Retrospective review

Setting—Tertiary referral center, ambulatory care

Interventions—Risedronate or zoledronate administration

Main outcome measures—Bone conduction pure tone threshold averages (PTA) and word recognition (WR) scores were examined for each ear before and after bisphosphonate treatment. Criteria for significant change were defined as greater than 10 decibels in PTA or between 4 to 18% in WR based on binomial variance.

Results—All 10 patients had audiometric progression of SNHL in the pre-treatment monitoring interval and 12 ears met criteria for significant progression. All 10 patients (19 ears) showed at least no significant progression of SNHL (i.e. stabilization) at an average follow up of 13 months. Two patients (3 ears) showed improvement by defined audiometric criteria. There were no major complications.

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Conclusion—Treatment with zoledronate or risedronate stabilized progressive SNHL related to otosclerosis in this small group of patients. Further evaluation of third generation bisphosphonate treatments is warranted.

Introduction

Otosclerosis is a disease of disordered bone metabolism affecting only the otic capsule. It is estimated to cause hearing loss in 0.3% of Caucasians, and most commonly presents as a conductive hearing loss[1, 2]. In addition to the well described conductive loss, patients with otosclerosis may develop sensorineural hearing loss[3,4], and clinicians estimate this to occur in 20 to 30% of patients[5]. Medications that reduce bone resorption have been employed in the past in an attempt to treat sensorineural hearing loss in otosclerosis by reducing the excess bone remodeling within the otic capsule. The results with sodium fluoride and first generation bisphosphonates, such as etidronate, have been modest [6,7], and therefore these medications are not universally employed. Currently, there remains no standard, clearly effective medical treatment for the sensorineural hearing loss associated with otosclerosis.

Over the past several years, nitrogen-containing bisphosphonates that offer more potent bone remodeling inhibition than early generation bisphosphonates have been developed. These bisphosphonates, including risedronate and zoledronate, are widely used in the treatment of metabolic bone diseases, such as osteoporosis, Paget's disease of the bone, osteogenesis imperfecta, and metastatic disease to bone [8]. The newer bisphosphonates utilize a different mechanism of action than early generation bisphosphonates, acting through inhibition of farnesyl pyrophosphate synthetase, an enzyme important for osteoclast function and survival[9]. There have been no previous reports on the clinical use of these newer bisphosphonates for reducing the progression of sensorineural hearing loss in patients with otosclerosis. We describe here 10 patients with accelerated sensorineural hearing loss documented by audiometry who elected therapy with the new generation bisphosphonates, risedronate and zoledronate, in an effort to stabilize their hearing. We demonstrate stabilization of progressive sensorineural hearing loss after treatment with these drugs, with no major complications of therapy identified.

Methods

After internal review board approval, the charts of all patients with otosclerosis and mixed hearing loss that were treated with systemic bisphosphonates between January 2008 and December 2009 at the Massachusetts Eye and Ear Infirmary were reviewed. This time period allowed for follow up of at least one year. Inclusion criteria for treatment were progression of the sensorineural component of hearing loss in at least one ear, surgical confirmation of the diagnosis of otosclerosis in one or both ears, and evidence of retrofenestral otosclerosis on computed tomography (CT). Retrofenestral otosclerosis was defined as extension of low-density lucencies around the cochlear capsule[10].

All patients were treated by both an otologist and a rheumatologist. Prior to medical treatment, a rheumatologist evaluated each patient to ensure his or her understanding of the medications offered, the rationale for treatment, and to elicit his or her preferences. Zoledronate, a parenteral third generation bisphosphonate, was preferentially used to ensure adequate dosing, since it obviates problems with variable absorption[11]. In patients who preferred oral therapy, risedronate was prescribed. Three patients opted for oral therapy and were treated with risedronate (patients 1,4 and 6). Treatment regimens were based on standard dosing regimens for osteoporosis. There has been no equivalency study between the zoledronate and risedronate regimens used, but both regimens have been shown to be

effective in osteoporosis, and both demonstrate a reduction in bone turnover markers in clinical trials[8,12]. Zoledronate was given by infusion as a single 5 mg dose, and risedronate was dosed as 35 mg weekly by mouth. Charts were reviewed for side effects from bisphosphonates.

All available audiograms for each patient were reviewed for word recognition (WR) scores, and bone conduction pure tone thresholds at five frequencies (250, 500, 1000, 2000, 4000 Hz). When thresholds were so high that word recognition testing could not be reliably tested due to limits of the loudness of the equipment, the word recognition score was listed as “could not test”.

The first available audiogram was compared to the audiogram immediately preceding bisphosphonate treatment (“immediate pre-treatment” audiogram) to determine progression of hearing loss. Additionally, the audiogram performed closest to one year prior to treatment (“one year pre-treatment” audiogram) was compared to the immediate pre-treatment audiogram to determine hearing progression in this one year prior to treatment. The immediate pre-treatment audiogram was then compared to the audiogram performed closest to one year following bisphosphonate treatment (“post-treatment” audiogram) to evaluate for progression, stabilization, or improvement of hearing loss. The audiologic data for both ears of each patient is presented.

The bone conduction pure tone average (BC-PTA) was calculated by averaging pure tone bone conduction thresholds for 500Hz, 1KHz, 2KHz, and 4KHz. When there was no response at the upper limit of bone conduction testing due to the limits of the equipment, the value plus 5 dB was included in the pure tone average. This previously described technique captures the large magnitude of the response by extrapolation and better estimates the pure tone average[13]. The rates of change of the WR and BC-PTA *before* treatment were calculated by subtracting the score on the first available audiogram from the score on the immediate pre-treatment audiogram, and dividing by the elapsed time interval. The rates of change of the WR and BC-PTA *after* treatment were calculated by subtracting the score on the immediate pre-treatment audiogram from the score on the post-treatment audiogram, and dividing by the elapsed time interval. Significant change in pure tone average was defined as change greater than 10 dB. Significant change in word recognition score was defined using a binomial model of variance, with significant change varying from 4% to 18% depending on the starting value[14,15].

Results

There were 10 consecutive patients who were treated with bisphosphonates in the given time period (Table 1). There were 6 men and 4 women, with ages ranging from 31 to 73 years old. Useful audiologic data was available for only 19 ears, because patient 10 had suffered a profound sensorineural hearing loss in the right ear after a stapedectomy more than 20 years prior to the study period. All audiograms were performed at the Massachusetts Eye and Ear Infirmary, with the exception of the first available audiogram for patient 5.

Two or more pre-treatment audiograms were available to establish progression of sensorineural hearing loss for all patients, except patients 1 and 10 (Table 1). For patients 1 and 10, the otologist had documented progressive sensorineural hearing loss based on his review of multiple pre-treatment audiograms, although only the immediate pre-treatment audiograms were available for this study. Patients 2–9 were followed for 6.8 to 153.5 months (average of 80.7 months) prior to initiation of bisphosphonate therapy, as calculated by the time interval between the first available audiogram and the immediate pre-treatment audiogram. During this period, all patients had progressive sensorineural hearing loss in one

or both ears, at one or more frequencies or by word recognition score. Observations over this period prompted recommendation by the otologist for bisphosphonate treatment. More specifically, ears 3R, 3L, 5R, 5L, 6R, 6L, 7R, 7L, 8R, 8L, 9R, 9L had available audiometric data demonstrating significant progression of sensorineural hearing loss (significant as defined in the methods section). Ear 10R had a pre-existing profound sensorineural hearing loss with no response at the limits of audiometry and thus progression could not be assessed in this ear. For ear 2R, the air conduction pure tone average was 100 decibels (dB) at the time of the first available audiogram, likely leading to a low word recognition score due to the limits of the equipment. A stapedectomy was performed for ear 2R, which lowered air conduction thresholds significantly and likely contributed to perceived improvement in the word recognition score during the pre-treatment time period.

One year pre-treatment audiograms were available for patients 2, 3, 4, 5, 6, and 7, and audiologic data from these audiograms is included in Table 1. The average time prior to treatment for the one year pre-treatment audiograms was 11.9 months, with a range of 6.5 to 15.4 months.

All patients underwent non-contrast temporal bone computed tomography imaging. The imaging demonstrated lucencies consistent with fenestral and retrofenestral otosclerosis in all 10 patients. Findings were bilateral in all patients, except patient 6. In ear 6R, fenestral but not retrofenestral lucencies consistent with otosclerosis were noted.

All patients underwent a stapedectomy on at least one ear. Most of these surgeries occurred in the interval between the first available audiogram and the immediate pre-treatment audiogram, as noted in Table 1. Two ears (2R and 9R) underwent a revision stapedectomy during the follow up period after bisphosphonate treatment and before the post-treatment audiogram. Three ears (1R, 5L, and 10R) had undergone a stapedectomy in the remote past, prior to the study period. Based on comparison of immediate pre-surgery and post-surgery audiograms, there was no significant change in bone conduction pure tone average or word recognition score after stapedectomy surgeries performed during the study period.

Patients 2 and 5 received more than one administration of zoledronate. For patient 2, the post-treatment audiogram included in the tables and figures was performed after the first dose of zoledronate (but before the second dose of zoledronate). Notably, patient 2 had further improvement in her sensorineural hearing after the second dose of zoledronate. The word recognition and bone conducted pure tone average for patient 2 at 1.2 months before the second dose of zoledronate was 42% and 68 dB for the right ear, and 82% and 63 dB for the left ear. An audiogram at 5.5 months after the second dose of zoledronate reported 66% and 63 dB for the right ear, and 82% and 56 dB for the left ear. For patient 5, no immediate pre-treatment audiogram was available for the first and second doses of zoledronate; thus the included audiograms are before and after the third dose of zoledronate.

There was considerable variability among patients in the extent of hearing loss prior to and after bisphosphonate treatment. Therefore, the complete audiometric data for all ears from the pre-treatment and post-treatment audiograms is presented in Table 2a. Due to the broad range of hearing loss among patients, median WR and bone conduction PTA scores were calculated rather than averages. All patients with available audiograms at each of four timepoints (patients 2–7) were included in the median scores. The median WR score at the first available, 1 year pre-treatment, immediate pre-treatment, and post-treatment audiogram was 95%, 90%, 81%, and 88%, respectively. The median PTA at the first available, 1 year pre-treatment, immediate pre-treatment, and post-treatment audiogram was 35 dB, 44 dB, 45 dB, and 49 dB, respectively. The average time period between the pre-treatment audiogram and bisphosphonate treatment was 3.4 months (ranging from 0.3 to 8.3 months). The

average follow up period (i.e. time after administration of the bisphosphonate and before the post-treatment audiogram) was 13.1 months (ranging from 8.8 to 18.8 months). The outcome for each individual ear is presented in Figure 1.

The rate of change of WR and BC-PTA during the approximately one year time interval before and after treatment is presented in Table 2b. There was significant variability between patients in rates of change before and after treatment. The median WR score decreased by 3.7% per year prior to treatment, and increased by 5.5% per year after treatment. The median BC-PTA worsened by 4.3 decibels (dB) per year prior to treatment and by 1.0 dB per year after treatment.

All ears demonstrated either no significant change or improvement in both bone conduction pure tone averages and word recognition scores in the post-treatment period. These results were summarized in Table 3 by applying definitions of stable, improved, or worse to each ear. For WR scores, significant change was based on a binomial model of variance and varied from 4 to 18 % depending on the starting value. For PTA, a change greater than 10 dB was considered significant.

There were no major side effects or complications related to bisphosphonate administration. One patient reported a minor side effect of intermittent headaches that lasted for one week after zoledronate infusion.

Discussion

This is the first study of risedronate and zoledronate treatment for progressive sensorineural hearing loss in otosclerosis. Our observation of 10 patients reveals stabilization in word recognition scores and bone conduction pure tone averages in all, with improvement in two patients. Clinically, this has translated into an improved quality of life for these individuals, with no significant adverse consequences of treatment noted.

Histopathologic study suggests that sensorineural hearing loss in otosclerosis is associated with involvement of the endosteal layer of the otic capsule, which leads to deposition of connective tissue or “hyalinization” of the spiral ligament [16,17,18,19]. Pharmaceutical treatments that reduce bone resorption have, therefore, been pursued as a possible treatment for the progressive sensorineural hearing loss seen in otosclerosis. Sodium fluoride was a widely used medical treatment for otosclerosis in the latter half of the twentieth century. Several studies have shown a modest reduction in the progression of sensorineural hearing loss with fluoride treatment [6,20,21,22, 23,24], and since the side effects are generally benign, fluoride continues to be employed for treatment of otosclerosis in some centers.

Over the past several decades, bisphosphonates, which are compounds with high bone binding affinity and powerful anti-resorptive properties, have become part of the standard treatment for metabolic bone disease. These drugs have been used in osteoporosis, Paget’s disease of bone, osteogenesis imperfecta and metastatic bone disease to inhibit bone remodeling in an effort to protect the structural integrity of bone [8,25]. Few reports exist on the treatment of sensorineural hearing loss in otosclerosis with bisphosphonates[7,26]. The only published double-blinded placebo-controlled study of bisphosphonate treatment used etidronate, one of the first generation bisphosphonates[7]. This trial failed to show a significant reduction in the progression of hearing loss, but did note a trend toward significance with etidronate treated patients. The study was also limited because bone conduction threshold data was available for only five of the fourteen etidronate treated patients.

More recently, third generation, nitrogen-containing, heterocyclic bisphosphonates such as risedronate and zoledronate have been introduced, and these compounds have shown the most powerful anti-resorptive properties[9]. These newer agents are potent antiresorptive agents at doses that do not impair mineralization of bone, a problem inherent in etidronate. To our knowledge, there have been no prior published studies of risedronate and zoledronate treatment for progressive sensorineural hearing loss in otosclerosis.

We suspected that bisphosphonate treatment would be more likely to slow or halt progression of sensorineural hearing loss, rather than improve already existing hearing loss. Therefore, patients with audiometrically documented progressive sensorineural hearing loss were selectively offered treatment at the discretion of the treating otologist. Although this adds bias and represents a limitation of a retrospective study, it allows evaluation of results after a shorter time period (e.g. the 13 month average follow up in this study). For patients not already experiencing progression of sensorineural hearing loss, changes might not be seen for five to ten years given the slow progression of the disease. This is one of the inherent challenges of evaluation of medications that reduce progressive sensorineural loss in this disease.

It is important to note that this is a retrospective study with a small number of patients. Because of the small number of patients and broad range of hearing losses pre and post treatment, evaluation of individual patient outcomes is more important than group statistics. Although we calculated median scores, complete audiologic data and individual patient audiologic data over time was also presented. In this study, patients functioned as their own controls by comparing the pre-treatment hearing progression to post-treatment hearing progression. When using patients as their own controls, results must be interpreted with the caveat that there may be variability in the disease course over time for each patient. In otosclerosis, this variability may be attributed to changes in the disease state from active to quiescent, and vice versa. Averages and median values for word recognition scores and pure tone averages were calculated in order to summarize the audiometric findings. Summary statistics should be interpreted with caution when combining a small group of patients with a broad range of hearing losses, and thus the complete audiometric data and individual patient outcomes are presented.

Differences in time intervals before and after treatment may add bias to the results of a retrospective study. In this study, *all* available audiometric data prior to treatment was presented in order to illustrate the long term progression of hearing loss for each patient prior to treatment. Furthermore, decisions by both physicians and patients were based on the long term trend in hearing prior to treatment, not just the one year pre-treatment interval. In order to allow comparison of comparable time intervals (i.e. one year prior and one year after treatment), data from audiograms done approximately one year prior to treatment was also presented. Furthermore, the *rate* of change of WR and BC-PTA was presented in order to minimize bias related to differences in pre and post-treatment time intervals. Examination of the rate of change per year alone, however, fails to demonstrate the progressive nature of the sensorineural hearing loss prior treatment. The slow progression of the disease represents an inherent challenge to the study of sensorineural hearing loss in otosclerosis and its treatment.

We recognize that including both ears for each patient is a possible confounding factor. Thus, although averaged word recognition scores and pure tone averages are presented, we also urge readers to evaluate the complete audiologic data presented for each ear in Table 2.

Stapedectomy surgery can result in worsening of word recognition scores or bone conducted hearing thresholds, but this was not seen for any patients that underwent stapedectomy

during the study period. In ear 2R, which underwent stapedectomy during the pre-treatment interval, a significant increase in word recognition score was noted after surgery. This was likely due to improvement of the air conduction thresholds so that more accurate testing of word recognition could be performed.

In this study, all medications were administered by a rheumatologist, after a discussion of risks and benefits. Prior to beginning treatment, all patients were informed that this is an “off-label” use of bisphosphonate medications. Although no patients in this study suffered any major side effects or complications related to bisphosphonate treatment, the risks of systemic bisphosphonate treatment must be considered in the decision to treat patients with otosclerosis. Furthermore, patients remain at risk for some side effects or complications beyond the average 13 month follow up period reported in this study. Reported adverse effects seen in patients treated for osteoporosis include headache, arthralgia, renal damage, hypocalcemia, atrial fibrillation, osteonecrosis of the jaw, atypical femoral fractures, and erosive esophagitis, ulceration, and bleeding with oral administration [8,27,28]. An atypical femoral fracture is a fatigue fracture caused by repeated loading at a site with small cracks or fissures. Since these small cracks would normally be repaired by bone remodeling, patients treated with systemic bisphosphonates may be at higher risk of atypical femoral fractures. Multiple studies have shown an increase in atypical femoral fractures in bisphosphonate treated patients, although the absolute risk is still very small[8,29]. An acute phase reaction has been reported to occur in up to 20% of patients treated with intravenous bisphosphonate administration results in fever, weakness, bone pain and myalgia[8]. There have also been case reports of both sudden and progressive hearing loss after pamidronate and etidronate administration[30,31], although the rarity of this event makes it difficult to be certain that the hearing loss was truly related to bisphosphonate administration. Further, bisphosphonates must be used with caution in women of child-bearing potential, given the long half-life of these drugs in bone and the ability of these drugs to pass through the placenta.

Because of the risks with systemic treatment and ongoing clinical investigations of optimal bisphosphonate dosing and duration in metabolic bone diseases, it is important that bisphosphonate treatment be administered by a rheumatologist or other clinician familiar with these drugs. Since bisphosphonates remain bound to bone for long periods of time [9], it may not be necessary to continue bisphosphonate treatment beyond the first dose or first several years. Further studies are needed to determine the optimal treatment duration for patients with osteoporosis and osteopenia [8, 32], and both long term efficacy and safety must be considered when deciding whether to continue treatment. This study does not aim to evaluate the efficacy or safety of bisphosphonates long term for otosclerosis, but we would implore a thorough consideration of the risks and benefits when considering bisphosphonate treatment beyond several years. In the future, systemic side effects could be avoided with local delivery of bisphosphonates to the inner ear. Prior to implementation of any local treatment, the safety and ototoxicity, as well as the effective doses and duration of treatment, should be evaluated in animal models.

Conclusion

This pilot study demonstrates stable sensorineural hearing during an average 13 month follow up after zoledronate or risedronate treatment in otosclerosis patients with cochlear involvement and some progression of sensorineural hearing loss during the year or years prior to treatment. Remarkably, two patients showed significant improvement in sensorineural hearing after bisphosphonate treatment. Importantly, no patients had significant worsening of hearing in the post-treatment interval. Further evaluation of third generation bisphosphonates for sensorineural or mixed hearing loss in patients with otosclerosis is

worthwhile. It is imperative that patients understand the possible complications with systemic bisphosphonate treatment, and that bisphosphonates be administered by a clinician familiar with the drug class.

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References

1. Ealy M, Smith RJ. Otosclerosis. *Adv Otorhinolaryngol*. 2011; 70:122–129. [PubMed: 21358194]
2. Chole RA, McKenna M. Pathophysiology of otosclerosis. *Otol Neurotol*. 2001 Mar; 22(2):249–257. [PubMed: 11300278]
3. Cureoglu S, Baylan MY, Paparella MM. Cochlear otosclerosis. *Curr Opin Otolaryngol Head Neck Surg*. 2010 Oct; 18(5):357–362. [PubMed: 20693902]
4. Topsakal V, Fransen E, Schmerber S, Declau F, Yung M, Gordts F, et al. Audiometric analyses confirm a cochlear component, disproportional to age, in stapedial otosclerosis. *Otol Neurotol*. 2006 Sep; 27(6):781–787. [PubMed: 16885785]
5. Glorig, AG.; Gallo, R. Comments on sensorineural hearing loss in otosclerosis. In: Schuknecht, HF., editor. *Otosclerosis*. Boston: Little, Brown; 1962. p. 63-78.
6. Cruise AS, Singh A, Quiney RE. Sodium fluoride in otosclerosis treatment: review. *J Laryngol Otol*. 2010 Jun; 124(6):583–586. [PubMed: 20163750]
7. Kennedy DW, Hoffer ME, Holliday M. The effects of etidronate disodium on progressive hearing loss from otosclerosis. *Otolaryngol Head Neck Surg*. 1993 Sep; 109(3 Pt 1):461–467. [PubMed: 8414563]
8. Favus MJ. Bisphosphonates for osteoporosis. *N Engl J Med*. 2010 Nov 18; 363(21):2027–2035. [PubMed: 21083387]
9. Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int*. 2008 Jun; 19(6):733–759. [PubMed: 18214569]
10. Sakai, O.; Curtin, HD.; Hasso, AN.; Swartz, JD. Otosclerosis and dysplasias of the temporal bone. In: Som, PM.; Curtin, HD., editors. *Head and neck imaging*. 4th ed. St. Louis: Mosby; 2002. p. 1245-1273.
11. Russell RG. Bisphosphonates: the first 40 years. *Bone*. 2011 Jul; 49(1):2–19. [PubMed: 21555003]
12. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA*. 1999 Oct 13; 282(14):1344–1352. [PubMed: 10527181]
13. Halpin, C. Measuring audiometric outcomes. In: Shin, J.; Hartnick, C.; Randolph, G., editors. *Evidence based otolaryngology*. New York: Springer; 2008. p. 227-238.
14. Halpin C, Rauch SD. Using audiometric thresholds and word recognition in a treatment study. *Otol Neurotol*. 2006 Jan; 27(1):110–116. [PubMed: 16371857]
15. Thornton AR, Raffin MJ. Speech-discrimination scores modeled as a binomial variable. *J Speech Hear Res*. 1978 Sep; 21(3):507–518. [PubMed: 713519]
16. Kelemen G, Linthicum FH Jr. Labyrinthine otosclerosis. *Acta Otolaryngol Suppl*. 1969; 253:1–68. [PubMed: 5267215]
17. Kwok OT, Nadol JB Jr. Correlation of otosclerotic foci and degenerative changes in the organ of Corti and spiral ganglion. *Am J Otolaryngol*. 1989 Jan-Feb; 10(1):1–12. [PubMed: 2929871]
18. McKenna, MJ.; Merchant Saamil, N. Disorders of Bone. In: Merchant, SN.; Nadol, Joseph B., Jr, editors. *Schuknecht's Pathology of the Ear*. 3rd ed. USA: People's Medical Publishing House; 2010.
19. Parahy C, Linthicum FH Jr. Otosclerosis: relationship of spiral ligament hyalinization to sensorineural hearing loss. *Laryngoscope*. 1983 Jun; 93(6):717–720. [PubMed: 6190061]

20. Bretlau P, Causse J, Causse JB, Hansen HJ, Johnsen NJ, Salomon G. Otospongiosis and sodium fluoride. A blind experimental and clinical evaluation of the effect of sodium fluoride treatment in patients with otospongiosis. *Ann Otol Rhinol Laryngol*. 1985 Mar-Apr;94(2 Pt 1):103–107. [PubMed: 3888030]
21. Bretlau P, Salomon G, Johnsen NJ. Otospongiosis and sodium fluoride. A clinical double-blind, placebo-controlled study on sodium fluoride treatment in otospongiosis. *Am J Otol*. 1989 Jan; 10(1):20–22. [PubMed: 2655462]
22. Shambaugh GE Jr, Scott A. Sodium Fluoride for Arrest of Otosclerosis; Theoretical Considerations. *Arch Otolaryngol*. 1964 Sep;80:263–270. [PubMed: 14172805]
23. Derks W, De Groot JA, Raymakers JA, Veldman JE. Fluoride therapy for cochlear otosclerosis? an audiometric and computerized tomography evaluation. *Acta Otolaryngol*. 2001 Jan; 121(2):174–177. [PubMed: 11349772]
24. Causse JR, Causse JB. Clinical studies on fluoride in otospongiosis. *Am J Otol*. 1985 Jan; 6(1):51–55. [PubMed: 2579565]
25. Russell RG. Bisphosphonates: The first 40years. *Bone*. 2011 Jul; 49(1):2–19. [PubMed: 21555003]
26. Brookler KH, Tanyeri H. Etidronate for the neurotologic symptoms of otosclerosis: preliminary study. *Ear Nose Throat J*. 1997 Jun; 76(6):371–376. 9–81. [PubMed: 9210803]
27. Novartis Pharmaceutical Corporation. East Hanover, New Jersey: 2011. Reclast [Full Prescribing Information]. Available at: <http://www.pharma.us.novartis.com/product/pi/pdf/reclast.pdf>
28. Warner Chilcott LLC. Rockaway, New Jersey: 2011. Actonel [Full Prescribing Information]. Available at: http://www.actonel.com/global/prescribing_information.pdf
29. Schilcher J, Michaelsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. *N Engl J Med*. 2011 May 5; 364(18):1728–1737. [PubMed: 21542743]
30. Yasil S, Comlekci A, Guneri A. Further hearing loss during osteoporosis treatment with etidronate. *Postgrad Med J*. 1998 Jun; 74(872):363–364. [PubMed: 9799894]
31. Reid IR, Mills DA, Wattie DJ. Ototoxicity associated with intravenous bisphosphonate administration. *Calcif Tissue Int*. 1995 Jun; 56(6):584–585. [PubMed: 7648491]
32. Boonen S, Ferrari S, Miller PD, Eriksen EF, Sambrook PN, Compston J, Reid IR, Vanderschueren D, Cosman F. Postmenopausal osteoporosis treatment with antiresorptives: Effects of discontinuation or long-term continuation on bone turnover and fracture risk-a perspective. *J Bone Miner Res*. 2012 May; 27(5):963–974. [PubMed: 22467094]

Figure 1.

A and B show bone conduction pure tone average (BC-PTA) and word recognition score (WR) in the pre-treatment interval. C and D show BC-PTA and WR in the post-treatment interval. Each point on the graph represents one ear. The black line is a reference line that marks no change between the first available and the immediate pre-treatment audiograms in A and B, and between the immediate pre-treatment and post-treatment audiograms in C and D. Change is not considered significant within the shaded area, with significance defined by more than 10 dB change in PTA (A and C) or by the binomial model of variance for WR (B and D). The majority of the ears are below the line in A and B. In contrast, most ears after treatment, as shown in C and D, are close to the line or above the line.

Table 1

Patient information and pre-treatment audiologic data

Pt/ Side	Age/ Sex	Word Recognition (1st Avail/ 1 Yr Pre/ Immed Pre)	Bone Conduction Pure Tone Average (1st Avail/ 1 Yr Pre/ Immed Pre)	Stapedectomy btw 1st Avail and Immed Pre	Treatment
1R	56 M	-/-/98	-/-/34	no	Ris for 4 wks then Zol
1L		-/-/54	-/-/46	yes	
2R	55 F	24/42/54	65/69/68	yes	Zol × 2
2L		78/72/72	54/64/60	no	
3R	54 F	98/86/76	36/50/59	yes	Zol
3L		98/70/80	34/51/73	no	
4R	36 M	76/76/76	48/51/44	yes	Ris
4L		94/94/90	30/30/33	no	
5R	52 F	92/100/82	36/35/44	no	Zol × 3
5L		92/80/74	36/35/48	no	
6R	31 F	98/98/96	20/39/43	yes	Ris
6L		96/98/98	25/49/46	no	
7R	45 M	98/98/94	11/21/25	no	Zol
7L		98/98/96	11/30/28	yes	
8R	54 M	72/-/38	50/-/68	yes	Zol
8L		72/-/28	59/-/68	no	
9R	52 M	98/-/94	15/-/41	yes	Zol
9L		98/-/82	20/-/35	no	
10R	73 M	-/-/CNT	*	no	Zol
10L		-/-/CNT	-/-/65	yes	

* Profound sensorineural hearing loss occurred 20 years previously after stapedectomy, "n" = not available, CNT=could not test due to limits of the equipment, Pt= patient, R=right, L=left, 1st Avail= first available audiogram, 1 Yr Pre= audiogram closest to one year prior to treatment, Immed Pre =audiogram immediately prior to treatment, Zol= zoledronate, mo= months, "x 2"= for 2 doses

Table 2

a. Audiometry before and after bisphosphonate treatment													
Pt/Side	Before Bisphosphonate Treatment						After Bisphosphonate Treatment						
	250	500	1000	2000	4000	WR(%)	250	500	1000	2000	4000	WR(%)	
1R	15	20	30	25	60	98	25	25	25	25	40	98	
1L	25	25	50	55	55	54	15	15	10	40	70	96	
2R	35	65	75	65	65	54	45	60	70	65	75	42	
2L	30	55	60	60	65	72	25	55	65	70	60	82	
3R	20	55	55	55	70	76	20	55	55	55	65	84	
3L	>45	>65	75	75	70	80	40	>65	70	70	70	70	
4R	15	15	35	50	75	76	5	10	35	70	65	86	
4L	5	10	25	40	55	90	0	10	30	50	60	94	
5R	15	20	20	50	>80	82	15	25	20	55	>80	90	
5L	10	30	20	55	>80	74	15	30	25	60	>80	82	
6R	25	35	45	45	45	96	35	45	55	45	45	98	
6L	30	45	45	45	50	98	30	45	60	45	45	98	
7R	10	15	5	25	55	94	10	20	10	35	55	96	
7L	5	10	5	40	55	96	5	20	10	35	50	100	
8R	25	50	70	>70	75	38	15	35	35	55	70	78	
8L	15	35	65	>75	>85	28	20	40	65	>75	75	56	
9R	5	15	35	55	60	94	5	10	20	45	60	92	
9L	10	20	15	50	55	82	5	15	15	45	60	92	
10R	-	-	-	-	-	CNT	-	-	-	-	-	CNT	
10L	>30	>50	>60	>70	>80	CNT	25	50	55	>70	>80	28*	

b. Rate of change over one year before and after treatment				
Pt/ Side	WR (%/year)		BC-PTA (dB/year)	
	Before Tx	After Tx	Before Tx	After Tx
1R	-	0.0	-	-5.2

b. Rate of change over one year before and after treatment				
Pt/ Side	WR (%/year)		BC-PTA (dB/year)	
	Before Tx	After Tx	Before Tx	After Tx
1L	-	43.3	-	-12.4
2R*	-7.7	-0.8	1.3	
2L	0.0	6.4	-3.1	1.9
3R	-7.9	6.7	7.2	-0.8
3L	7.9	-8.3	17.5	-2.5
4R	0.0	11.5	-7.0	1.2
4L	-7.0	4.6	5.2	5.8
5R	-15.5	10.9	7.8	2.7
5L	-5.2	10.9	11.2	2.7
6R	-1.7	1.5	3.5	3.7
6L	0.0	0.0	-2.6	2.2
7R	-7.4	1.9	7.4	4.8
7L	-3.7	3.8	-3.7	1.0
8R	-	44.7	-	-21.2
8L	-	31.3	-	-3.4
9R	-	-1.9	-	-6.5
9L	-	9.4	-	-0.9
10R	-			
10L	-			-0.8
Median	-3.7	5.5	4.3	1.0

Values are pure tone bone conduction thresholds for the given frequency (in Hertz). WR= word recognition using a 50 item assay. CNT= could not test due to limits of the equipment

* interpret with caution because patient Arabic speaking

"-" not available

* excluded because WR testing limited by equipment

Table 3

Summary: Stable, improved, or worse after treatment?

Pt/Side	WR	PTA	Follow up (months)
1R	Stable	Stable	10
1L	Improved	Stable	
2R	Stable	Stable	19
2L	Stable	Stable	
3R	Stable	Stable	14
3L	Stable	Stable	
4R	Stable	Stable	10
4L	Stable	Stable	
5R	Stable	Stable	9
5L	Stable	Stable	
6R	Stable	Stable	16
6L	Stable	Stable	
7R	Stable	Stable	13
7L	Stable	Stable	
8R	Improved	Improved	11
8L	Improved	Stable	
9R	Stable	Stable	13
9L	Stable	Stable	
10R	CNT	*	15
10L	CNT	Stable	

Using criteria of >12% as significant change in word recognition and >10 dB as significant change in pure tone average. Follow up interval between bisphosphonate treatment and post-treatment audiogram. WR= word recognition, PTA= pure tone average, CNT=could not test because patient is Arabic speaking,

* profound sensorineural hearing loss after attempted stapedectomy 20 years prior to presentation