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RESEARCH ARTICLE

HAS DENOSUMAB PLACE IN TREATMENT OF OTOSCLEROSIS?

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Abstract

Background and aim: Otosclerosis is an inflammatory disease that causes bone resorption and deposition in auditory structures, leading to conductive and/or sensorineural progressive deafness.
The aim of the study was to evaluate the thesis of denosumab, a human monoclonal antibody against receptor activator of nuclear factor kappaB ligand, in treatment of otosclerosis.
Methods: A review of published papers related to the mechanism of action of denosumab.
Results: Denosumab increased bone affinity and demonstrated effectiveness in the treatment of osteoporosis and other metabolic bone diseases.
Conclusion: Denosumab, an essential mediator of osteoclastic bone resorption, is a promising therapeutic agent for the management of otosclerosis.

INTRODUCTION

Otosclerosis (OS) is a disease of disordered temporal bone metabolism affecting only the endochondral bone of the otic capsule [1]. The etiopathogenesis remains unclear and includes genetic predisposition, disturbed bone metabolism, persistent measles virus infection, autoimmunity, and hormonal and environmental factors [2].

The disease presents clinically in about 1% of Caucasians and is inherited as an autosomal dominant trait with incomplete penetrance. OS is the most common etiology of conductive hearing loss in 15-50 years old patients with intact tympanic membrane. Although, patients with OS may develop sensorineural hearing loss in 20 to 30%.In 1% of cases, the disease is considered purely cochlear, presenting with a sensorineural hearing loss only, as the OS involves areas other than the footplate. In practice OS is seen more often in women than men by the ratio of approximately 2:1. The prevalence of OS varies with race, and in Caucasians the disease is found in 7.3% and 10.3% of temporal bones for men and women respectively. The stapes appears fixed in only 12.3% of patients with histopathologic evidence of OS [2].
Histologic alterations of OS have been well described and are usually found in the pericochlear region, oval window, and stapes base. These alterations include areas of increased cellularity and bone resorption and deposition, characterized by the presence of osteoclasts and osteoblasts, increased vascularization, fibrous thickening of the mucosa, and tissue affinity for acid dyes. These alterations may coexist, so there are three histopathologic patterns: spongiotic-cellular, sclerotic-dense mineralized bone, and mixed, because the disease is dynamic. There are reports of OS in the ossicles and in the stapes superstructures represented by apparent reduction in the thickness of the cartilaginous cap top and slight evidence of remodeled bone, newly formed at the level of crura, presented by prominent cementitious lines and woven bone[3,4].

Clinical diagnosis is based on history, physical examination findings, and audiometry, and may be supported by imaging studies. The treatment of OS includes surgery, stapedectomy or stapedotomy, where the stapes superstructure is removed and is replaced by a prothesis, and medications such as sodium fluoride and first

generation bisphosphonates. The aim of medications is to reduce bone resoportion in an attempt to treat sensorineural hearing loss in OS by reducing the excess bone remodeling within the otic capsule [2].

Denosumab is a fully human monoclonal antibody that binds RANKL, preventing RANKL from activating RANK, its receptor on the osteoclast surface. With reduced RANK–RANKL binding, osteoclast formation, function and survival are inhibited, bone resorption decreases and bone mass increases [5,6].There have been no previous reports on the clinical use/results of denosumab for reducing the progression of sensorineural hearing loss in patients with OS.

METHODS

Published papers related to the mechanism of action of denosumab were sought through MEDLINE, PUBMED, GOOGLE SCOLAR searches.

RESULTS

Receptor activator of nuclear factor kappaB ligand(RANKL), a cytokine member of the tumor necrosis factor (TNF) superfamily, is an essential mediator of osteoclast formation, function, and survival. RANKL is expressed on the surface of osteoblasts and in soluble form after cleavage from the cell surface or secretion from T-cells. When RANKL binds to receptor activator of nuclear factor kappaB (RANK) on the cell surface of osteoclasts and preosteoclasts, it promotes osteoclast activation, differentiation, and survival, thereby increasing bone resorption. Osteoprotegerin (OPG), another member of the TNF receptor superfamily, is a soluble nonsignaling decoy receptor that binds to RANKL, preventing its interaction with RANK and inhibiting osteoclastogenesis and decreasing survival of existing osteoclasts [7,8].

An increase in the RANKL:OPG ratio has been implicated in the pathogenesis of osteoporosis in women and men, skeletal manifestations of rheumatoid arthritis and skeletal complication of other disorders [9,10,11]. RANKL has been identified as a potential target for therapeutic intervention in the treatment of these diseases [12,13]. Prevention of RANKL‐RANK interaction inhibits osteoclast formation, function, and survival; thereby decreasing bone resorption and interrupting cancer ‐induced bone destruction [14,15]. Possible strategies to down-regulate RANKL include inhibition of RANKL production, stimulation of endogenous OPG, and administration of exogenous OPG, soluble RANK (sRANK), or antibody to RANKL [14,16].

Denosumab, formerly known as AMG 162, is a novel antiresorptive treatment.
Denosumab is a fully human immunoglobulin G2monoclonal antibody with high affinity and specificity for human RANKLa member of the tumor necrosis factor family, blocks binding of RANKL, an essential factor in the terminal differentiation and activation of osteoclasts, to the RANK receptor found on the surface of osteoclasts and osteoclast precursors. Denosumab inhibits osteoclast differentiation, activity, and survival, and consequently, results in decreased bone resorption [7,8].

Denosumab follows nonlinear, dose‐ dependent pharmacokinetics. The bioavailability of one subcutaneous denosumab injection is 61% and serum concentrations are detected within 1 h. Maximal serum concentrations are achieved in 5-21 days and denosumab may be detectable for 9 months or longer. Based upon monoclonal antibody pharmacokinetics, denosumab is most likely cleared by the reticuloendothelial system with minimal renal filtration and excretion. The elimination half-life of denosumab is 32 days, and the terminal half-life is 5-10 days. Denosumab does not incorporate into bone [8].

FDA approves denosumab:

1) for the treatment of postmenopausal women with osteoporosis at high risk for facture(1 Jun 2010),
2) for the prevention of skeletal-related events in patient with bone metastases from solid tumors(19 Nov 2010)
3) for the treatment of bone loss in patients with prostate or breast cancer undergoing hormone ablation therapy(19 Sep 2011)
4) for the treatment of bone loss in men with osteoporosis at high risk factor for fracture(21 Sep2012)
5) to treat giant cell tumor of bone(13Jun 2013)
6) for hypercalcemia of malignancy refractory to bisphosphonate therapy(8 Dec 2014)

CONCLUSIONS

OS is a localized disease of the metabolism of endochondral bone of the otic capsule characterized by disordered resorption and subsequent bone deposition. The onset of the pathologic process takes place with the calcification of the annular ligament of the oval window, and by extension to the stapes footplate, causing its attachment, most commonly in the anterior portion, and then to the ossicular chain, leading to deafness.

The aim of medications in OS is to reduce bone resoportion in an attempt to treat sensorineural hearing loss 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 and therefore these medications are not universally employed. Currently, there is no standard, clearly effective medical treatment for the sensorineural hearing loss associated with OS available [17,18].

The nitrogen-containing bisphosphonates, including risedronate and zoledronate, are widely used in the treatment of metabolic bone diseases by acting through inhibition of farnesyl pyrophosphate synthetase, an enzyme important for osteoclast function and survival and have been reported as a hopefully new treatment of OS [17].

Denosumab is a fully human monoclonal antibody that works as antiresorptive agent by inhibiting RANKL and helping regulate turnover in healthy bone. Denosumab binds with high specificity and affinity to the cytokine RANKL, inhibiting its action; as a result, osteoclast recruitment, maturation and action are inhibited, and bone resorption slows [19,20]. In contrast to the bisphosphonates, denosumab does not become embedded within bone tissue. Rather, by binding to RANKL in the extracellular fluid and circulation, denosumab inhibits osteoclast formation, function and survival. As an antibody, denosumab is thought to be cleared from the bloodstream through the reticuloendothelial system, with a half-life of approximately 26 days, and it does not appear to induce the formation of neutralizing antibodies [17,18].

Denosumab is a promising therapeutic agent for the management of OS.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

[1] McKenna MJ, Merchant SN, Nadol, JB. Disorders of Bone In Schuknecht's Pathology of the Ear. Shelton, editors. People's Medical Pub. House-USA Inc; 2010.p.716-9.
[2] Thomas JP, Minovi A, Dazert S. Current aspects of etiology, diagnosis and therapy of otosclerosis. Otolaryngol Pol 2011; 65(3):162–170.
[3]Quesnel AM, Moonis G, Appel J, et al. Correlation of Computed Tomography with Histopathology in Otosclerosis. Otol Neurotol. 2013; 34(1):22-28.
[4]Carvalho B, Hamerschmidt R, Telles JE, et al. Anatomopathology of the Superstructure of the Stapes in Patients with Otosclerosis. Arch Otorhinolaryngol 2015; 19:1–4.
[5] Rizzoli R, Yasothan U, Kirkpatrick P. Denosumab. Nat Rev Drug Discov 2010; 9: 591–2.
[6]Lewiecki EM. Denosumab update. Cur Opin in Rheum 2009; 21:369–373.
[7] Hanley DA, Adachi JD, Bell A, et al. Denosumab: mechanism of action and clinical outcomes. Int J Clin Pract 2012; 66:1129-31.
[8]Narayanan P. Denosumab: A comprehensive review. SAJC 2013; 2:272-7.
[9]Min YK. Update on Denosumab Treatment in Postmenopausal Women with Osteoporosis. End Metab 2015; 30:19-26.
[10] Brown JP, Reid IR, Wagman RB, et al. Effects of up to 5 years of denosumab treatment on bone histology and histomorphometry: the FREEDOM study extension. J Bone Miner Res 2014; 29: 2051-6.
[11] Keaveny TM, McClung MR, Genant HK, et al. Femoral and vertebral strength improvements in postmenopausal women with osteoporosis treated with denosumab. J Bone Miner Res 2014; 29:158-65.
[12] Brown JP, Roux C, Torring O. Discontinuation of denosumab and associated fracture incidence: analysis from the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial. J Bone Miner Res 2013; 28:746-52.
[13]Watts NB, Roux C, Modlin JF, et al. Infections in postmenopausal women with osteoporosis treated with denosumab or placebo: Coincidence or causal association?
Osteop Int 2012; 23:327‑37.

[14] Lipton A, Goessl C. Clinical development of anti-RANKL therapies for treatment and prevention of bone metastasis. Bone 2011; 48: 96–9.
[15]Smith MR, Saad F, Coleman R, et al. Denosumab and bone‐metastasis‐free survival in men with castration‐resistant prostate cancer: Results of a phase 3,randomised, placebo‐controlled trial. Lancet 2012; 379:39‐46.
[16]Anastasilakis AD , Toulis KA, Polyzos SA, et al. RANKL inhibition for the management of patients with benign metabolic bone disorders. Exp Op on Invest Drugs. 2009; 18:1085–1102,.
[17]Quesnel AM, Seton M, Merchant SN, et al. Third generation bisphosphonates for treatment of sensorineural hearing loss in otosclerosis. Otol Neurotol. 2012; 33(8): 1308–1314.
[18]Baron R, Ferrari S, Russell RG, et al. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone 2011; 48: 677–92.
[19]Kyrgidis A, Tzellos TG, Toulis K et al. The Facial Skeleton in Patients with Osteoporosis: A Field for Disease Signs and Treatment Complications. J of Osteop. 2011;2011:147689. doi: 10.4061/2011/147689.
[20]Anastasilakis A.D., Toulis K.A., Goulis DG, et al. Efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis: a systematic review and a metaanalysis. Horm and Metab Res.2009 ;41:721–729.