Review Article

Role of odanacatib in reducing bone loss due to endodontic disease: An overview

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Abstract

Aims and Objectives: Through a comprehensive literature review, this article provides an overview of the potential role of odanacatib (ODN) in reducing bone loss due to endodontic disease. **Materials and Methods:** A literature review was performed in PubMed Central, MEDLINE, Cochrane Library, and EBSCO databases. The articles identified included those published between 2002 and 2016. Based on the predetermined inclusion and exclusion criteria, out of 237 articles found, 50 were selected for this review. **Results:** Cathepsin K (CstK), which is indispensible to the immune system, also plays an important role in osteoclastic bone resorption. ODN, which is an orally active, selective, and effective inhibitor of CstK, decreases bone resorption by selectively inhibiting proteolysis of matrix proteins by CstK, without affecting other osteoclastic activity or osteoblast viability. **Conclusion:** The goal of endodontic treatment is to achieve a clinically asymptomatic state along with formation of reparative bone. This process could take 6 months or longer, hence, an earlier reversal of the resorption process could lead to faster healing and resolution of the periapical lesion. Use of ODN can be of help in achieving this goal.

Key words: *Cathepsin K (Ctsk), cytokines, innate immunity, odanacatib (ODN), toll-like receptor (TLRs)*

INTRODUCTION

Bacterial infection of the pulp results in necrosis. The inflammatory products of the necrosed pulp find their way to the periapical area, which leads to immune inflammatory response. Innate host response initially involves recognition of microbes and production of inflammatory mediators. Toll-like receptors (TLRs) expressed by resident cells and leucocytes activate innate immune response by binding to various bacterial components.[1] After TLR activation, an intracellular signalling cascade is initiated, that involves activation of transcription factors, resulting in the production of inflammatory cytokines, leukocyte, and osteoclast migration.[2] Bar Shavit demonstrated that the activation of TLRs in osteoblast induces production of osteogenic cytokines.[3] Among these cytokines, TNF-α, IL-1, and IL-6 are predominant. TNF-α leads to cell migration towards the infected and inflamed site, inducing the upregulation of adhesion molecules and production of chemotactic chemokines.[4,5] It plays a central role in inflammatory reaction, bone resorption, and loss of connective tissue. It further upregulates the production of other proinflammatory innate immune cytokines such as IL-1β and IL-6.[4-6] The latter are involved in inflammatory cell migration and osteoclastogenic process.[6,7] Absence of innate immunity cytokines

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attenuates inflammatory bone loss but their simultaneous inhibition results in more effective protection leading to almost complete remission of bone loss.[7,8]

The goal of endodontic treatment is the removal of necrotic, infected pulp tissue to inhibit inflammatory reaction in the periapical tissue, resulting in the formation of reparative bone. The latter could take 6 months or longer, and hence an earlier reversal of the resorptive process would lead to faster healing and resolution of the periapical lesion. In clinical trials, odanacatib (ODN) has been found to decreases bone resorption and increase bone density. It is currently being developed as an oral therapeutic agent for the treatment of osteoporosis and is undergoing phase 3 clinical trials. In the treatment of periapical diseases with ODN, the trabecular bone has been found to remain un-affected, whereas the inflammatory cell infiltration decreases.[9] Through a comprehensive literature review, this article aims to provide an overview of the role of ODN in reducing bone loss due to endodontic diseases.

MATERIALS AND METHODS

Search criteria

Inclusion criteria

The search was limited to research studies and review articles published between 2002 and 2016. Restrictions were not placed regarding the study design and the language used.

Exclusion criteria

Thesis, letters, and informative articles were excluded. Articles published prior to 2002 were also excluded.

Search strategy

A literature review was performed in PubMed Central, MEDLINE, Cochrane Library, and EBSCO host. The articles identified included those published between 2002 and 2016 with the following subject headings terms and/or keywords in various combinations: development and prevention of bone loss, periapical inflammation, cathepsin K, and odanacatib. Based on the predetermined inclusion and exclusion criteria, out of the 237 articles found, 50 were selected for this review [Table 1].

DISCUSSION

Development of bone loss in periapical area

Bone loss and bone formation is an ongoing phenomenon throughout life. It occurs within discrete units called bone remodelling units (BMUs). Osteoclasts and osteoblasts are active at specific times within each BMU. Receptor Activator for Nuclear factor k B Ligand (RANKL) is produced by osteoblasts and is regulated by osteotropic hormones such as PTH and calcitriol, as well as cytokines such as IL6. RANKL plays an important role in osteoclast differentiation, activation, and survival. The binding of RANKL to its receptor, expressed in mononuclear hematopoietic precursors, initiates the process that ultimately leads to the formation of multinuclear osteoclast.

Pulpal necrosis arising from bacterial infection leads to periapical inflammation. The resultant periapical lesion displays infiltration of inflammatory cells, predominantly macrophages and T cells[10] in conjunction with the production of proinflammatory cytokines.[11,12] Bone homeostasis is dependent upon the continuation of equilibrium between bone resorption by osteoclasts and bone formation by osteoblasts. Origin of osteoclast is from the hematopoietic precursors of monocyte, i.e., macrophage. They remain in the bone marrow and move from peripheral circulation into the bone on instructions of chemokines. Various chemokines such as MCP-1/CCL2, and SDF-1α/CXCL12 tend to bring about osteoclast chemotaxis and differentiation, however, their activation is achieved only with RANKL.[13] The MIP-1α/CCL3 induces adhesion of osteoclast to primary osteoblasts. The MIP-1γ/CCL9 is dominant in the survival of osteoclast. RANKL effect plays a role in the survival of osteoclast depending on the ability to induce MIP-1γ/CCL9 production.[13] T cells by virtue of RANKL and IFN-γ production regulate osteoclastogenesis.[14] Surface of the activated T cells displays RANKL that activates bone resorbing cells. RANKL acts by binding to its Receptor Activator of Nuclear factor k B (RANK), which is a cell-surface protein. The latter is present on osteoclast precursor cells. On activation, it leads to osteoclast maturation.[15] RANK activates TNF receptor associated factor 6 (TRAF 6), c- Fos, and calcium signalling pathways, resulting in the induction and activation of NFATc1 (nuclear factor of activated T cells c1). The latter is the all-important factor for osteoclastogenesis.[14] In periapical granuloma, Vernal *et al*. established a direct relationship between high RANKL level and monocytes activity, leading to periapical bone destruction.[15]

Osteoprotegerin (OPG) or osteoclastogenesis inhibitory factor (OICF) acts as the natural decoy receptor for RANKL. Balance between OPG and RANKL regulates osteoclast formation.[16] OPG by

Table 1: Description and summary of all included literature data

S. No.	Author	Year	Study design	Finding/Summary
1	Kassem *et al.*[1]	2016	*In-vitro* study	TLR activates innate immune response.
2	Zhao *et al.*[4]	2016	*In-vitro* study	TNF helps in the production of chemokines.
3	Khan *et al.*[13]	2016	*In-vitro* study	MIP-1γ/CCL9 induces adhesion of ostooclast to primary osteoblast and helps in the survival of osteoclast.
4	Liu *et al.*[16]	2016	*In-vivo* study	Equilibrium between OPG and RANKL governs osteoclast formation. Level of RANKL in periapical lesion is higher than healthy periapical tissue.
5	Hao *et al.*[9]	2015	*In-vivo* study	ODN reduces bone resorption along with reduced number of inflammatory cells. ODN inhibits CtsK reducing bone loss through osteoclast inhibition, decreased activation, and differentiation.
6	Hao *et al.*[27]	2015	*In-vivo* study	CtsK has important role in bone resorption and immune system. ODN can inhibit endodontic disease development, bone erosion, and immune response.
7	Gamsjager and Resch[30]	2015	*In-vivo* study	CtsK inhibitors do not bind to bone for producing action.
8	Boggild[36]	2015	Review	ODN does not reduce the number of osteoclast.
9	Wei *et al.*[37]	2015	*In-vitro* study	ODN reduces bone resorption while preserving bone formation.
10	Chen *et al.*[2]	2014	*In-vitro* study	TLR activation results in the production of cytokines and osteoclast migration.
11	Yang *et al.*[5]	2014	*In-vivo* study	TNF helps in the production of chemokines.
12	Marton and Kiss[10]	2014	Review	Periapical lesion has a predominance of macrophages and T cells. Bone loss is induced in periapical area due to infection from root apex.
13	Aranjo Piress *et al.*[11]	2014	*In-vitro* study	Proinflammatory cytokines are produced in the periapical lesion.
14	Komatsu *et al.*[14]	2014	*In-vivo* study	T cells govern osteoclastogenesis through production of RANKL and IFN-γ. Former is the master transcriptor for osteoclastogenesis.
15	Walsh and Choi[17]	2014	Review	RANK/RANKL/OPG trio regulates bone remodelling and osteoclast activation.
16	Duong[24]	2013	Review	CtsK plays an important role in bone resorption in periapical area.
17	Gao *et al.*[26]	2013	*In-vivo* study	Ctsk has key role in bone resorption in inflammation mediated bone resorption diseases such as periapical diseases. Inhibition of CtsK inhibits bone resorption but osteoclast differentiation is affected only partially.
18	Cusik *et al.*	2012	*In-vivo* study	Bone resorption resulting from activity of osteoclast is inhibited by ODN, without decreasing their count. In trabecular bone, where inhibition of bone resorption is associated with reduction in bone formation, release of growth factors from bone matrix is found.
19	Masarachia *et al.*	2012	*In-vivo* study	In trabecular bone, where inhibition of bone resorption is associated with reduction in bone formation, release of growth factors from bone matrix is found.
20	Khosla[42]	2012	Commentary	ODN reduces bone resorption without disrupting communication between non-resorbing osteoclast and osteoblast.
21	Silva *et al.*	2012	*In-vivo* study	T cells infiltrating periapical region express RANKL and endodontic bacteria induce RANKL expression leading to the development of bone resorptive periapical lesions.
22	Ng *et al.*	2012	*In-vitro* study	ODN by inhibiting CtsK prevents bone resorption.
23	Garlet *et al.*	2012	Review	Several cytokines present protective and destructive role in periapical inflammation.
24	Schett[39]	2011	Review	Cytokines are secreted from periapical inflammatory cells, which govern osteoclast, in turn controlling bone loss.
25	Eisman *et al.*[38]	2011	*In-vitro* study	ODN selectively inhibits CtsK but does not inhibit osteoclast viability or activity.
26	Hellstein *et al.*	2011	Review	RANKL is the principal final mediator of osteoclastic bone resorption. Prevention of RANKL from binding to its receptor on osteoclast prevents bone resorption.
27	Grannaite *et al.*	2011	Review	Cytokines lead to periapical bone resorption.
28	Eastell *et al*	2011	In-vivo study	CtsK inhibitors have rapid onset and resolution for the anti resorptive effect.
29	Garlet[18]	2010	Review	OPG reduces bone destruction (in periapical lesion) by stopping induction of RANKL.

Contd...

Table 1: Contd...

S. No.	Author	Year	Study design	Finding/Summary
30	Black[34]	2010	Review	Balicatib possess properties of lysosomotropism.
31	Isabel *et al.*[35]	2010	*In-vitro* study	CtsK inhibitors are susceptible to interactions with other drugs due to metabolization by enzymes.
32	Sims[41]	2010	Review	Release of growth factors from bone matrix is reduced with decreasing bone resorption, while communication between non-resorbing osteoclast and osteoblast is not affected.
33	Fonseca *et al.*[7]	2009	Review	Inflammatory cytokines lead to osteoclastogenic process and their inhibition leads to remission of bone loss.
34	Podgorski[33]	2009	Review	Relacatib interacts with paracetamol, ibuprofen and atorvastatin. It is metabolized by enzymes, such as cytochromes, making them susceptible for interaction with other drugs.
35	Bar-Shavit[3]	2008	Review	Activation of TLR induces the production of osteogenic cytokines.
36	Graves[6]	2008	Review	TNF regulates production of other proinflammatory cytokines, which are involved in inflammatory cell migration and osteoclastogenic process.
37	Menezes *et al.*[19]	2008	*In-vitro* study	OPG restricts bone loss in periapical lesion by non-induction of RANKL.
38	Asagiri *et al.*[28]	2008	*In-vitro* study	Cathepsin is required for expression of TLR in dendritic cell. It regulates microbial byproducts and activates defence response. CtsK regulates immune and inflammatory response.
39	Russell *et al.*[31]	2008	Review	Concentration of CtsK within resorption lacunae is relevant for their activity.
40	Conchran[40]	2008	Review	Proinflammatory cytokines and chemokines can inhibit CtsK.
41	Fujisaki *et al.*[23]	2007	*In-vitro* study	Production of CtsK is upregulated by RANKL, TNF, and other agents, whereas it is downregulated by estrogen.
42	Chen *et al.*[29]	2007	*In-vitro* study	CtsK deficiency leads to compromised bone resorption (as in osteopetrosis).
43	Kumar *et al.*[32]	2007	*In-vivo* study	Relacatib has similar inhibitory potential for CtsK, L, and V, and selectively against CtsS and B.
44	Vernal *et al.*[15]	2006	*In-vivo* study	RANKL acts by binding to RANK and promotes osteoclast maturation, leading to periapical bone destruction.
45	Zhao *et al.*[21]	2005	*In-vivo* study	Cysteine proteinases under acidic conditions, within the resorption lacunae resorb bone.
46	Tolar *et al.*[20]	2004	Review	Cysteine proteinases under acidic conditions, within the resorption lacunae resorb bone.
47	Vaaraniemi *et al.*[22]	2004	*In-vitro* study	CtsK causes bone resorption by acting within the resorption lacunae.
48	Granes and Cochran[8]	2003	*In-vitro* study	Inhibition of cytokines results in remission of bone loss.
49	Radics *et al.*[12]	2003	*In-vivo* study	Proinflammatory cytokines are produced in periapical lesion.
50	Troen[25]	2002	Review	CtsK plays an important role in bone resorption.

binding to the receptors on RANKL deny the latter the opportunity of binding with RANK, preventing RANKL-mediated osteoclast maturation. Bone remodelling is thus regulated by the RANK/RANKL/OPG trio and is responsible for the development and activation of osteoclast.[17] Pro-inflammatory cytokines play a fundamental role in periapical bone destruction through induction of RANKL, whereas OPG synthesis attenuates lesion progression.[18,19]

Osteoclast by adhering to the surface of the bone, create "resorption lacuna." These result in resorption of bone. Towards the bone surface, they have ruffled border, delineated by clear zone. As the resorption lacuna becomes acidic, resorption is triggered. The acidic pH demineralizes the bone. Matrix proteins such as type I collagen are thus exposed and acted upon by enzymes such as cathepsin. The latter are cysteine proteinases, which become active in an acidic environment.[20,21]

RANKL directly induces osteoclast differentiation and activation, whereas its soluble decoy- receptor osteoprotegerin (OPG) neutralizes such osteoclastogenic effects. The level of RANKL mRNA expression in human periapical lesion is significantly higher than healthy periapical tissue,[15,16] indicating that locally produced RANKL also leads to periapical bone resorption. The exact mechanism underlying increase of RANKL in the periapical lesion leading to bone resorption is unclear.

Cathepsin K

Cathepsin K (CtsK), the predominant cysteine protease is produced in osteoclast and plays an essential role

in osteoclast function and degradation of protein components of the bone matrix. In actively resorbing osteoclast, CtsK is localized at the ruffled border and discharged into the extracellular surface when the lysomal vesicles fuse with the cell membrane to degrade Type I and II collagen within the acidic microenvironment of resorption lacunae.[22] The production of CtsK is downregulated by estrogen and upregulated by RANKL and TNF among other agents capable of increasing osteoclast formation and differentiation, such as Vitamin D, PTH, and interleukins.[23]

The inflammatory process magnifies in the apical area of the root canal and periapical region, resulting in periapical bone loss.[10] In this process, CtsK plays an important role.[24,25] Inhibition of osteoclast-expressed enzyme CtsK reduces bone resorption due to pulpal infection. CtsK is crucial in normal bone remodelling, osteoporosis, osteoarthritis, and periapical diseases.[26] The role of CtsK in bone resorption has been confirmed in humans. It also plays an important role in the immune system.[27] Asagiri *et al*. found that cathepsin is essential in dendritic cells for expression of TLR 9,[28] which leads to the regulation of microbial products and activation of defence responses.[28]

Inhibition of Cathepsin K

CtsK deficiency in humans and mice leads to osteopetrosis (pycnodysostosia) with highly compromised bone resorption due to the inability to degrade the collagen matrix of bone.[29] Therefore, direct targeting of osteoclast may be the most effective strategy for inhibiting bone loss. The level of cytokines shows reduced levels in periapical tissue in CtsK treated animals. Asagiri *et al*. found Ctsk to regulate immune and inflammatory responses.[28]

CtsK inhibitors have to be delivered into the lysosomes and they do not bind to bone for enforcing their activity.[30] Their activity is linked to their concentration in the resorption lacunae.[31] Inhibition of CtsK leads to diminished extracellular acidification and inhibits bone resorption; however, osteoclast differentiation is affected only partially.[26]

For inhibition of CtsK various agents have been used. Relacatib was used earlier. It has equivalent inhibitory potential for CtsK, L, and V and partial for CtsS and B.[32] Its use was discontinued following drug interactions with paracetamol, ibuprofen, and atorvastatin.[33] Another selective inhibitor of Ctsk, possessing property of lysosomotropism, and balicatib,[34] was also tried but adverse dermatologic effects resulted in discontinuation as well. CtsK inhibitors are prone to drug interactions as a result of being metabolized by enzymes such as cytochrome CYP3A4.[33,35]

Odanacatib

ODN is orally active, selective, effective, and reversible inhibitor of CtsK. It prevents bone resorption, arising out of the activity of osteoclast. It does not decrease the number of osteoclasts[36] rather decreases the magnitude of bone resorption and maintains the bone formation at the same time.[9,37] It selectively inhibits proteolysis of matrix protein by CtsK, without affecting other osteoclast activities or viability,[38] with simultaneous inhibition of inflammation. This in turn decreases osteoclast activation and differentiation, which shows a promising therapeutic method on periapical inflammatory disease.

Periapical inflammatory cells secrete various cytokines (IL-1α, TNF-α, IL-6, IL-11), which activate apoptosis of osteoclast, thus controlling bone resorption.[39] Suppression of CtsK tends to affect immune response because pre-osteoclasts are activated by RANKL, produced by osteoblast, T, and B cells. The latter can be activated by proinflammatory cytokines and chemokines such as IL-1, IL-6, TNF-α, and IL-17.[40] In the periapical disease, innate immunity results in activated macrophages that through cytokines bring about bone resorption. Inhibition of CtsK impairs adaptive immune response by decreasing the number of T cells. Number of oestoblast also decreases, which results in lower proinflammatory cytokine production, leading to lower osteoclast activation and differentiation.[9]

Growth factor release out of the bone matrix is diminished as a result of decreased bone resorption, whereas interaction between non-resorbing osteoclast and osteoblast may not be affected.[41,42] The net effect of CtsK inhibition on bone formation could depend on off-setting the effects of the loss of growth factor release from bone matrix with the ongoing effect of coupling factors from the increased numbers of relatively healthy osteoclast.

For endodontic success various criteria have been advocated over the years. Strindberg in 1956, Bender *et al*. in 1966, and Mor in 2004 have all been unanimous that, apart from being clinically asymptomatic, radiographically there should be restoration of normal periapical architecture or at least arrest or decrease in size of the periapical radiolucency

within 6 months to 2 years post treatment. ODN could be of help towards fulfilling this goal and achieving endodontic success.

CONCLUSION

Infected pulp tissue leads to inflammatory reaction in the periapical tissue, resulting in bone resorption. Bone remodelling is controlled by the RANK/RANKL/OPG trio. The latter controls the genesis and activation of osteoclasts. Osteoclasts get attached to the bone surface, creating "resorption lacuna." Because the latter becomes acidic, resorption is triggered. Inhibition of osteoclast-expressed enzyme, cathepsin K, inhibits bone resorption. Odanacatib, a highly selective and potent inhibitor of CtsK, can be of help towards achieving this goal because of its ability to inhibit osteoclast-mediated bone resorption while preserving bone formation and other osteoclast activities or viability. Thus, the use of ODN can lead to faster resolution of bone resorptive process, as a result of pulpal and periapical disease.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kassem A, Lindholm C, Lerner UH. Toll-Like Receptor 2 Stimulation of Osteoblasts Mediates *Staphylococcus Aureus* Induced Bone Resorption and Osteoclastogenesis through Enhanced RANKL. PLoS One 2016;11:e0156708.
2. Chen Q, Hou T, Luo F, Wu X, Xie Z, Xu J. Involvement of toll-like receptor 2 and pro-apoptotic signaling pathways in bone remodeling in osteomyelitis. Cell Physiol Biochem 2014;34:1890-900.
3. Bar-Shavit Z. Taking a toll on the bones: Regulation of bone metabolism by innate immune regulators. J Autoimmun 2008;41:195-203.
4. Zhao R, Wang X, Feng F. Upregulated Cellular Expression of IL-17 by CD4+ T-Cells in Osteoporotic Postmenopausal Women. Ann Nutr Metab 2016;68:113-8.
5. Yang S, Zhu L, Xiao L, Shen Y, Wang L, Peng B, *et al.* Imbalance of interlukin-17 + T-cell and Foxp3+ regulatory T-cell dynamics in rat periapical lesions. J Endod 2014;40:56-62.
6. Graves DT. Cytokines that promote periodontal tissue destruction. J Periodontol 2008;79:1585-91.
7. Fonseca JE, Santos MJ, Canhao H, Choy E. Interleukin-6 as a key player in systemic inflammation and joint destruction. Autoimmun Rev 2009;8:538-42.
8. Graves DT, Cochran D. The contribution of interleukin-1 and tumor necrosis factor to periodontal tissue destruction. J Periodontol 2003;74:391-401.
9. Hao L, Chen W, McConnell M, Zheng, Li S, Reddy M, *et al.* A small molecule, Odanacatib, inhibits inflammation and bone loss caused by endodontic disease. Infect Immun 2015;83:1235-45.
10. Marton IJ, Kiss C. Overlapping protective and destructive regulatory pathways in apical periodontitis. J Endod 2014;40:155-63.
11. Araujo-Pires AC, Francisconi CF, Bigurtti CC, Cavalla F, Aranha AM, Letra A, *et al.* Simultaneous analysis of T helper subsets (Th1, Th2, Th9, Th17, Th22, Tfh, Tr1 and Tregs) marker expression in periapical lesions reveals multiple cytokine clusters accountable for lesions activity and inactivity status. J Appl Oral Sci 2014;22:336-46.
12. Radics T, Kiss C, Tar I, Marton IJ. Interleukin-6 and granulocyte-macrophage colony-stimulating factor in apical periodontitis: Correlation with clinical and histologic findings of the involved teeth. Oral Microbiol Immunol 2003;18:9-13.
13. Khan UA, Hashimi SM, Bakr MM, Forwood MR, Morrison NA. CCL2 and CCR2 are Essential for the Formation of Osteoclasts and Foreign Body Giant Cells. J Cell Biochem 2016;117:382-9.
14. Komatsu N, Okamoto K, Sawa S, Nakashima T, Oh-hora M, Kodama T, *et al.* Pathogenic conversion of Foxp3+ T cells into TH17 cells in autoimmune arthritis. Nat Med 2014;20:62-8.
15. Vernal R, Dezerega A, Dutzan N, Chaparro A, Leon R, Chandia S, *et al.* RANKL in human periapical granuloma: Possible involvement in periapical bone destruction. Oral Dis 2006;12:283-9.
16. Liu Y, Du H, Wang Y, Liu M, Deng S, Fan L, *et al.* Osteoprotegerin-Knockout Mice Developed Early Onset Root Resorption. J Endod 2016;42:1516-22.
17. Walsh MC, Choi Y. Biology of the RANKL-RANK-OPG System in Immunity, Bone, and Beyond. Front Immunol 2014;5:511.
18. Garlet GP. Destructive and protective roles of cytokines in periodontitis: A reappraisal from host defense and tissue destruction viewpoints. J Dent Res 2010;89:1349-63.
19. Menezes R, Garlet TP, Letra A, Bramante CM, Campanelly AP, Figueira RC, *et al.* Differential patterns of receptor activator of nuclear factor kappa B ligand/osteoprotegerin expression in human periapical granulomas: Possible association with progressive or stable nature of the lesions. J Endod 2008;34:932-8.
20. Tolar J, Teitelbaum SL, Orchard PJ. Osteopetrosis. N Engl J Med 2004;351:2839-49.
21. Zhao H, Kitaura H, Sands MS, Ross FP, Teitelbaum SL, Novack DV. Critical role of beta3 integrin in experimental postmenopausal osteoporosis. J Bone Miner Res 2005;20:2116-23.
22. Väääräniemi J, Halleen JM, Kaarlonen K. Intracellular machinery for matrix degradation in bone-resorbing osteoclasts. J Bone Miner Res 2004;19:1432-40.
23. Fujisaki K, Tanabe N, Suzuki N, Kawato T, Takeichi O, Tsuzukibashi O, *et al.* Receptor activator of NF-kappaB ligand induces the expression of carbonic anhydrase II, cathepsin K, and matrix metalloproteinase-9 in osteoclast precursor RAW264.7 cells. Life Sci 2007;80:1311-8.
24. Duong LT. Inhibition of cathepsin K: Blocking osteoclast bone resorption and more. IBMS BoneKEy 2013;10:130-2.
25. Troen BR. The role of cathepsin K in normal bone resorption. Drug News Perspect 2002;17:19-28.
26. Gao B, Chen W, Hao L, Zhu G, Feng S, Ci H, *et al.* Inhibiting periapical lesions through AAV-RNAi silencing of cathepsin K. J Dent Res 2013;92:180-6.
27. Hao L, Chen J, Zhu Z, Reddy MS, Mountz JD, Chen W, *et al.* Odanacatib, A Cathepsin K- specific Inhibitor, Inhibits Inflammation and Bone loss caused by Periodontal Diseases. J Periodontol 2015;86:972-8.
28. Asagiri M, Hirai T, Kunigami T, Kamano S, Gober H-J, Okamoto K, *et al.* Cathepsin K-dependent Toll-like receptor 9 signaling revealed in experimental arthritis. Science 2008;319:624-7.
29. Chen W, Yang S, Abe Y, Li M, Wang Y, Shao J, *et al.* Novel pycnodysostosis mouse model uncovers cathepsin K function as a potential regulator of osteoclast apoptosis and senescence. Hum Mol Genet 2007;16:410-23.
30. Gamsjager M, Resch H. Cathepsin K antagonist: Preclinical and clinical data. Wien Med Wochenschr 2015;165:65-70.
31. 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;19:733-59.
32. Kumar S, Dare L, Vasko-Moser JA. A highly potent inhibitor of cathepsin K (relacatib) reduces biomarkers of bone resorption both *in vitro* and in an acute model of elevated bone turnover *in vivo* in monkeys. Bone 2007;40:122-31.

33. Podgorski I. Future of anticathepsin K drugs: Dual therapy for skeletal disease and atherosclerosis? Future Med Chem 2009;1:21-34.
34. Black WC. Peptidomimetic inhibitors of cathepsin K. Curr Top Med Chem 2010;10:745-51.
35. Isabel E, Bateman KP, Chauret N. The discovery of MK-0674, an orally bioavailable cathepsin K inhibitor. Bioorg Med Chem Lett 2010;20:887-92.
36. Boggild MK, Gajic-Veljanoski O, McDonald-Blumer H, Ridout R, Tile L, Josse R, *et al*. Odanacatib for the treatment of osteoporosis. Expert Opin Pharmacother 2015;16:1717-26.
37. Wei XX, Chu JP, Zou YZ, Ru N, Cui SX, Bai YX. Effect of odanacatib on root resorption and alveolar bone metabolism during orthodontic tooth movement. Genet Mol Res 2015;14:17972-81.
38. Eisman JA, Bone HG, Hosking DJ, McClung MR, Reid IR, Rizzoli R, *et al*. Odanacatib in the treatment of postmenopausal women with low bone mineral density: Three-year continued therapy and resolution of effect. J Bone Miner Res 2011;26:242-51.
39. Schett G. Effects of inflammatory and anti-inflammatory cytokines on the bone. Eur J Clin Invest 2011;41:1361-6.
40. Cochran DL. Inflammation and bone loss in periodontal disease. J Periodontol 2008;79:1569-76.
41. Sims NA. EPHs and ephrins: Many pathways to regulate osteoblasts and osteoclasts. Bonekey Osteovision 2010;7:304-13.
42. Khosla S. Odanacatib: Location and timing are everything. J Bone Miner Res 2012;27:506-8.