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

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Received: 22-09-16 Accepted: 12-12-16 Published: 30-12-16

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 indispensable 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 (TLR)

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.[6,7] The latter are involved in inflammatory cell migration and osteoclastogenic process.[8] Absence of innate immunity cytokines

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How to cite this article: Bahuguna R, Jain A, Khan SA, Arvind MS. Role of odanacatib in reducing bone loss due to endodontic disease: An overview. J Int Soc Prevent Communit Dent 2016;6:S175-81.
attenuates inflammatory bone loss but their simultaneous inhibition results in more effective protection leading to almost complete remission of bone loss.[28]

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 NFAE1 (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]
RANKL is the principal final mediator of osteoclastic bone resorption. TLR activation results in the production of cytokines and osteoclast activation.

Cytokines lead to periapical bone resorption. ODN reduces bone resorption while preserving bone formation. In trabecular bone, where inhibition of bone resorption is associated with reduction in bone formation, release of growth factors from bone matrix is found.

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Table 1: Contd...

| No. | Author                | Year | Study design | Finding/Summary                                      |
|-----|-----------------------|------|--------------|------------------------------------------------------|
| 30  | Black                  | 2010 | Review       | Balicitab possess properties of lysosomotropism.     |
| 31  | Isabel et al           | 2010 | In-vitro     | CtsK inhibitors are susceptible to interactions with other drugs due to metabolization by enzymes. |
| 32  | Sims                   | 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          | 2009 | Review       | Inflammatory cytokines lead to osteoclastogenic process and their inhibition leads to remission of bone loss. |
| 34  | Podgorski              | 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             | 2008 | Review       | Activation of TLR induces the production of osteogenic cytokines. |
| 36  | Graves                 | 2008 | Review       | TNF regulates production of other proinflammatory cytokines, which are involved in inflammatory cell migration and osteoclastogenic process. |
| 37  | Menezes et al          | 2008 | In-vitro     | OPG restricts bone loss in periapical lesion by non-induction of RANKL. |
| 38  | Asagiri et al          | 2008 | In-vitro     | CtsK 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          | 2008 | Review       | Concentration of CtsK within resorption lacunae is relevant for their activity. |
| 40  | Conchran               | 2008 | Review       | Proinflammatory cytokines and chemokines can inhibit CtsK. |
| 41  | Fujisaki et al         | 2007 | In-vitro     | Production of CtsK is upregulated by RANKL, TNF, and other agents, whereas it is downregulated by estrogen. |
| 42  | Chen et al             | 2007 | In-vitro     | CtsK deficiency leads to compromised bone resorption (as in osteopetrosis). |
| 43  | Kumar et al            | 2007 | In-vivo      | Relacatib has similar inhibitory potential for CtsK, L, and V, and selectively against CtsS and B. |
| 44  | Vernal et al           | 2006 | In-vivo      | RANKL acts by binding to RANK and promotes osteoclast maturation, leading to periapical bone destruction. |
| 45  | Zhao et al             | 2005 | In-vivo      | Cysteine proteinases under acidic conditions, within the resorption lacunae resorb bone. |
| 46  | Tolar et al            | 2004 | Review       | Cysteine proteinases under acidic conditions, within the resorption lacunae resorb bone. |
| 47  | Vaaraniemi et al       | 2004 | In-vitro     | CtsK causes bone resorption by acting within the resorption lacunae. |
| 48  | Granes and Cochran     | 2003 | In-vitro     | Inhibition of cytokines results in remission of bone loss. |
| 49  | Radics et al           | 2003 | In-vivo      | Proinflammatory cytokines are produced in periapical lesion. |
| 50  | Troen                  | 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. Pro-inflammatory cytokines play a fundamental role in periapical bone destruction through induction of RANKL, whereas OPG synthesis attenuates lesion progression.

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.

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, 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 lysosomal 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 (pynodysostosia) 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 osteblast 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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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