Review Article

Current Approaches in Dental Alveolar Abscess in Sight of Bone Related Drugs

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ARTICLE INFO

ABSTRACT

Dentoalveolar abscess, a localized accumulation of pus in the alveolar bone, can produce significant changes in alveolar bone proper that may be resulted by dental caries, trauma or pulpitis causing alveolar bone resorption or even loss. Unfortunately, it can extend vertically toward the apex of the tooth. Additionally, a periapical abscess may form in the alveolar bone adjacent to the apex of the tooth. Interestingly, many bacterial products can stimulate osteoclast formation and bone resorption of periapical tissues. This review displayed drugs that can affect bone resorption that classified as (1) Osteoclast inhibitors such as: bisphosphonates, gene therapeutic (Cathepsin K) estrogens, selective estrogen receptor modulators (SERMs), calcitonin monoclonal antibodies such as denosumab and (2) Osteoclast activators such as DMP-PYT, nuclear factor-Kappa B (RANK) signaling and adrenomedullin.

Introduction

Dental or dentoalveolar abscess is a localized accumulation of pus in the alveolar bone apically to the tooth. It may occur secondary to dental caries, trauma, deep fillings or failed root canal treatment. Bacteria and microorganisms entering the periapical tissues via the apical foramen, these bacteria can induce acute inflammation leading to pus formation. The pathogenesis of dentoalveolar abscess is polymicrobial in nature, comprising of various facultative anaerobes, such as the viridans group *streptococci* and the *Streptococcus anginosus* group, and strict anaerobes, especially anaerobic cocci, *Prevotella* and *Fusobacterium* species [1]. Pulpitis is an inflammation of dental pulp and may also result in alveolar bone loss. It may result from trauma, thermal shock, chemical stimulus or mishaps procedures of dental pulp, but most often reflects invasion of dental caries into the pulp chamber. If inflammatory products come through the pulp canal, it will produce a local inflammatory reaction in the alveolar bone near to the apex of the tooth, called osteomyelitis, which, can result in a periapical abscess [2].

Dental abscess can produce significant changes in alveolar bone proper [2]. Alveolar bone is one of three tissues which support the tooth; the others are the periodontal ligament and the cementum. Alveolar bone is formed by intramembranous bone formation of the mandible and maxilla [1]. Periodontal disease starts as inflammation in the gingival tissues. If it was untreated, it will spread to the PDL and alveolar bone. Therefore, advanced periodontal disease results in significant alveolar bone loss. It may include a single tooth but will include adjacent teeth. Alveolar bone loss can extend vertically toward the apex of the tooth. In this case, a periapical abscess may form in the alveolar bone adjacent to the apex of the tooth. Many bacterial products of some of these microorganisms can stimulate osteoclast formation and bone resorption of periapical tissues [3].

In fact, there was a highly relation between numbers and types of bacteria and number of osteoclastic cells in dental abscess. On the other hand, there was an osteogenic cells which found in the infected dental field to conserve the remaining healthy bone and produce newly bone cells which reduce spread of infection all over the bone of maxilla or mandible [3]. In view of drugs that can affect bone resorption, it could be classified into: Osteoclast inhibitors and Osteoclast activators.

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I Osteoclast Inhibitors

Antiresorptive therapies are used to increase bone strength in case of osteoporosis and are classified into: bisphosphonates, gene therapeutic (Cathepsin K) estrogens, selective estrogen receptor modulators (SERMs), calcitonin monoclonal antibodies such as denosumab [4].

i Cathepsin K

A novel approach of gene therapeutic using recombinant adeno-associated virus (AAV)-mediated RNAi knockdown of Cathepsin K (Ctsk) gene expression, was used to target osteoclasts and periapical bone resorption *in vivo*. It was reported that AAV-sh- Cathepsin K (AAV-sh-Ctsk) capable to impair osteoclast function *in vivo* and reduce bacterial infection-stimulated bone resorption by 88% [5]. Interestingly, a decrease in mononuclear leukocyte infiltration and inflammatory cytokine expression was accompanying the reduced periapical lesion size. Literatures revealed that AAV-RNAi silencing of Cathepsin K in periapical tissues can significantly lower bone destruction, endodontic disease development, and inflammation in the periapical lesion [5].

ii Bisphosphonates

Bisphosphonates are a class of drugs that prohibit bone resorption and are involved in treatment of metabolic diseases like osteoporosis, hypercalcaemia of malignancy, Paget's disease and multiple myeloma [6]. Bisphosphonates chemical structure consists of two phosphate group attached by single carbon atom [7]. This class is classified into: nitrogen containing and non-nitrogen containing type. Although they are the standard treatment of choice for skeletal problems such as osteoporosis, other bone disorders and certain forms of malignancy, the use of antiresorptive therapy has been implicated in the pathoetiology of osteonecrosis of the jaw, which is a painful and debilitating condition [8]. Those containing nitrogen showed potential activity along with accumulation of maximum concentration in the matrix and osteoclasts [9].

The mechanism of action is explained by that bisphosphonates possess a high affinity toward bone minerals and can bind strongly to hydroxyapatite leading to selective uptake to the target organ and high concentration in bone, particularly at the sites of active bone remodeling. Furthermore, they inhibit the osteoclast differentiation, reducing their activity, and inducing osteoclast apoptosis [10]. Currently, there is no effective treatment for bisphosphonate induced osteonecrosis, so prevention is extremely important. Precautions should be taken in consideration with patients who are at the risk of development of osteonecrosis of jaw (ONJ) especially with dental surgical procedure like extractions, retrograde apicoectomies, periodontal surgery and implant placement is contemplated [11].
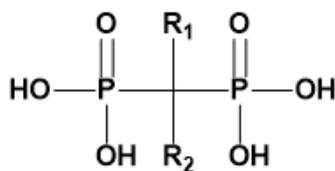

Bisphosphonates

iii Estrogens

Estrogens can work through blocking cytokine signals in order to activate osteoclasts that in turn suppress bone resorption and leads to increased bone strength. Exogenous estrogens were the main therapy for osteoporosis prevention in postmenopausal women to reduce the risk of vertebral and hip fractures [12]. Literatures reported that women who used hormone replacement therapy had a 33% reduction in vertebral fractures and a 40% reduction in hip fractures compared with control women [13].

iv Selective Estrogen Receptor Modulators (SERM)

They have estrogen agonist activity at bone to inhibit bone resorption through the same mechanism as do estrogens. Raloxifene is the most widely used SERM in osteoporosis treatment [14]. Interestingly, no significant reduction was observed in the risk of fractures at nonvertebral sites in either raloxifene study. The major safety concern of raloxifene therapy is related to its association with increased risks of venous thromboembolism, pulmonary embolism and fatal stroke [15]. Raloxifene treatment was not associated with death from any cause or with the total risk of stroke [14]. Other SERMs, such as basedoxifene and lasofoxifene reduce the risk of vertebral fractures in postmenopausal women with osteoporosis as well as nonvertebral fractures in women with osteoporosis aged 59–80 years [16, 17].
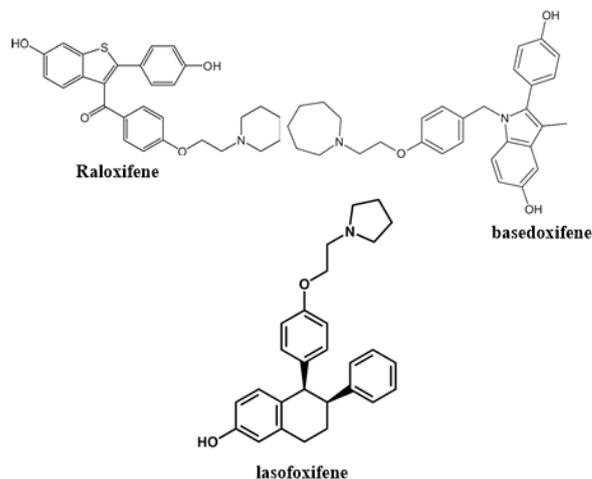
v Calcitonin

Calcitonin, a 32-amino-acid endogenous peptide hormone, works through inhibition of bone resorption by binding to osteoclasts through a high-affinity receptor. However, the reduction in bone turnover associated with calcitonin treatment is much smaller than that seen with other antiresorptive agents [18]. Calcitonin also seems to have an analgesic effect on acute painful vertebral fractures [19].

vi Denosumab

Denosumab, a new antiresorptive agent, is a fully human monoclonal antibody that inhibits RANKL, a protein required for osteoclast formation, function and survival [20]. On the basis of this evidence of antifracture efficacy, denosumab appears to be another promising first-line osteoporosis therapy, although (as with any new agent) long-term safety data are required to establish its role in patient care [21].

II Osteoblast Activators

i DMP-PYT

Small molecules were isolated that activated both SMADs and β-catenin, that led to the discovery of a novel potent osteogenic compound, DMP-PYT. They worked through BMP2 stimulation, DMP-PYT substantially increased osteoblast differentiation through enhanced expression of osteoblast-specific genes and accelerated calcification featured by activation of BMPs expression [22]. DMP-PYT promoted BMP2-induced SMAD1/5/8 phosphorylation and β-catenin expression, the latter in a BMP2-independent manner. DMP-PYT alone enhanced nuclear localization of β-catenin to promote the DNA-binding and transcriptional activity of T-cell factor, thereby resulting in increased osteoblast differentiation in the absence of BMP2 [22].

DMP-PYT
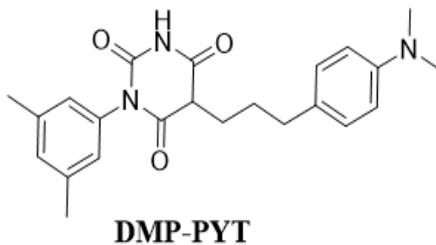
ii Nuclear Factor-Kappa B (RANK) Signaling

Bone remodeling involves osteoclast activation, resorption, and reversal, prior to osteoblast migration into the bone pit. The Receptor Activator of NF-kB (RANK) signaling pathway plays an important role in bone remodeling. Two components of the RANK signaling pathway, RANK Ligand (RANKL) and the decoy receptor Osteoproteger in (OPG), are expressed predominantly on the surface of osteoblasts, while RANK is principally expressed on the surface of osteoclasts [23].

iii Adrenomedullin

Adrenomedullin is a potent stimulator of osteoblastic activity in vitro and in vivo. Adrenomedullin is a 52-amino acid vasodilator peptide produced in many tissues, including bone. It has 20% sequence identity with amylin, a regulator of osteoblast growth, and circulates in picomolar concentrations. Adrenomedullin also increased [3H] thymidine incorporation into cultured neonatal mouse calvaria. Adrenomedullin stimulated phenylalanine incorporation into both isolated osteoblasts and calvaria [24].

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