

ALENDRONATE IN PERIODONTICS : WHERE ARE WE

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ABSTRACT:

Periodontitis is a multifactorial disease involving bacterial biofilms and the generation of an inflammatory response. The latter causes the major part of the periodontal tissue breakdown. Alveolar bone resorption is a major component of the periodontal destruction observed in periodontitis. Novel treatment modalities of periodontitis intend to control and modulate the host response to bacterial aggression. Drugs such as bisphosphonates are proven antiresorptive agents that can potentially inhibit the alveolar bone resorption of bone by inhibiting osteoclasts and may have an effect on osteoblasts. They are structurally similar to pyrophosphate, a normal product of human metabolism. This structure gives the drugs a high affinity for bone and they probably remain in bone for many years. These bone specific properties could also provide an interesting management strategy to stimulate osteogenesis in conjunction with regenerative materials around endosseous implants. This review describes the mechanism of action and potential use of novel aminobisphosphonate alendronate in periodontal treatment.

Key words: Bone regeneration, bisphosphonates, alendronate, osteoclast, Periodontal diseases

INTRODUCTION:

The primary etiology of periodontal diseases and chronic inflammation around natural tooth and dental implants is a bacterial infection. The clinical course of periodontitis in patients can vary greatly

despite their harbouring similar quantitative and qualitative levels of bacteria. In essence, Gram negative infection of the pocket is necessary but not sufficient to induce the periodontal disease initiation and progression. Ultimately it is the host's reaction to

presence of bacteria that mediates tissue destruction. This response can be influenced by environmental (e.g., tobacco use), acquired (e.g., systemic disease), genetic and other risk factors. Since destruction of periodontium is believed to be due to host response, it is logical to consider therapeutic approaches that modulates host response in addition to anti bacterial approaches in management of periodontal diseases.

Techniques to improve bone regeneration have included the use of biologic mediators to improve the quantity and quality of the bone being regenerated. Non steroidal anti-inflammatory agents, subantimicrobial doses of doxycycline, bone morphogenic proteins, and growth factors have all been studied.^[1,2] Because prevention of periodontal bone loss is so important in maintaining a stable periodontium, the use of bisphosphonates (antiresorptive agents) have been evaluated for their effects on inhibiting bone loss resulting from periodontitis. Bisphosphonates (BPs) are chemical analogues of pyrophosphates and are completely resistant to hydrolysis (**Figure 1**).^[3] They bind to the hydroxyapatite crystals of bone and prevent both their growth and their dissolution. The proven efficacy of BPs to inhibit the osteoclastic bone resorption has led to their use in the management of periodontal diseases as a host modulating factor in the perspective of preventing the alveolar bone loss.^[4]

Alendronate (ALN), a second-generation bisphosphonate, includes

aminobisphosphonates with an amino-terminal (**Figure 2**).^[5] It is a potent inhibitor of bone resorption (six to 10 times more potent than pamidronate and up to 1000 times more potent than etidronate) and therefore used in low concentrations than etidronate and clodronate.^[6] Furthermore no inhibition of mineralization has been described at doses used pharmacologically. The net effect of alendronate on bone formation might be explained by its inhibition of osteoclasts, thus affecting bone maturation and remodeling. Once taken up by bone, alendronate has a prolonged skeletal retention (half life up to several years) and significant amounts can be released in the resorptive process which may in turn provide protection to the alveolar bone.^[7]

MECHANISM OF ACTION: ALENDRONATE:

Osteoclasts (bone-resorbing cells) are different from haematopoietic stem cells. After adhering to the bone surface, osteoclast develops a sealing zone and a ruffled border where protons (H⁺), cathepsin K and MMPs, respectively, are released to resorb the mineral part, as well as the organic matrix of the bone (**Figure 3**).^[8,9] An overproduction of osteoclasts by the fusion of their precursors and/or their activation by pro-inflammatory cytokines (IL-1b, TNF-a and PGE2) is responsible for the bone loss occurring in periodontal diseases.^[10] Therefore, the use of a drug that inhibits the osteoclast function and/or formation seems to be a promising issue in periodontal treatment.^[4]

Effect on osteoclasts:

After administration, bisphosphonates bind to the bone mineral. During the initiation of resorptive process by osteoclasts, bisphosphonates are released due to highly acidic local environment. These are then taken up by osteoclasts. Several modes of action have been investigated which include bisphosphonate mediated inhibition of the development of osteoclasts, induction of osteoclastic apoptosis, reduction of activity, and prevention of the development of osteoclasts from hematopoietic precursors. It has also been shown that the bisphosphonate ALN caused a rise in intracellular calcium levels in an osteoclast-like cell line.^[11] This finding is of great interest because it could suggest the presence of a receptor for bisphosphonates on osteoclasts. Inside the osteoclasts, they inhibit the enzyme(s) of the mevalonate pathway (**Figure 4,5**).^[12]

Effect on osteoblasts:

Osteoblasts could also mediate the activity of bisphosphonates, by inducing the production of an osteoclast-inhibitory factor.^[13] Bisphosphonates prevent osteocyte and osteoblast apoptosis, probably by interfering with the phosphorylated fraction of extracellular-signal-regulated kinases.^[14] Reports have demonstrated that bisphosphonates stimulate the formation of osteoblast precursors and mineralized nodules, thereby promoting early osteoblastogenesis.^[15] Consistent with the findings, bisphosphonates have been

recently shown to decrease the expression of the receptor activator of NF- κ B ligand (RANKL) and increase the expression of the RANKL decoy receptor osteoprotegerin (OPG) in human osteoblastic cells.^[16]

Other actions:

Since both osteoclasts and macrophages belong to the mononuclear phagocytic system, it is conceivable that bisphosphonates affect not only bone metabolism but also inflammatory responses. From this point of view, the effect of the alendronate on the transendothelial migration of human peripheral blood mononuclear cells (which is a central event in inflammatory reactions) has been studied; it has been concluded that alendronate has a distinct effect on the transendothelial migration of human peripheral blood mononuclear cells *in vitro*.^[17] nBPs are also shown to inhibit angiogenesis.^[18] This inhibition may not only be mechanism-based, but may also involve endothelial cell adhesion, migration, and survival.^[19] There is little evidence to indicate that nBPs directly and significantly inhibit angiogenesis *in vivo* as the effective concentrations, generally 10 micro Molar or greater, are difficult to achieve *in vivo* in non-skeletal tissue. Additionally ALN is thought to inhibit matrix metalloproteinases (MMPs), the enzymes involved in extracellular matrix (ECM) degradation in physiological and pathological diseases such as periodontitis through a mechanism that involves chelation of cations.^[20] Other data show that abrogation of interleukin-6

production by bisphosphonates in human osteoblastic cells can occur, which could also affect osteoclastic activity.^[21] At the cellular level bisphosphonates have been shown to increase biosynthesis of collagen and osteocalcin by bone cells and proteoglycans by cartilage cells. The effect on collagen may be partially due to impaired intracellular collagenolysis. Alendronate can increase colony formation of osteoblasts and the formation of mineralized nodules in human cell cultures in vitro, a phenomenon that is accompanied by an increased formation of basic fibroblast growth factor. It has been suggested that some of these effects may be mediated through protein-tyrosine phosphatases. Thus it is possible that bisphosphonates could, under certain circumstances, also act by increasing bone formation.^[22] In recent years, it has been suggested that bisphosphonates could inhibit prostaglandin synthesis in vitro.^[23]

ALENDRONATE IN PERIODONTAL THERAPY:

Alendronate was approved by the FDA in the USA in 1995 and is now applied extensively to prevent bone loss in women without osteoporosis, and also to reduce the incidence of vertebral and non-vertebral fracture and to increase bone mineral density (BMD). Several studies have reported the effectiveness of ALN in preventing alveolar bone destruction associated with periodontal disease when administered systemically or locally to the target site.

Systemic administration

Animal Studies:

One major research focus of BPs in periodontal therapy is the determination of their effect on bone resorption along with the clinical parameters in experimental animal models. Studies have shown an obvious benefit of BPs as adjuvants to the mechanical periodontal treatment that resulted in reduced alveolar bone resorption following systemic administration.^[24,25] In a histometric study, Simvastatin and ALN showed increase in density of tooth-supporting bone which was affected by estrogen deficiency.^[26] In some studies, it was shown that groups treated with alendronate, when administered intravenously biweekly at a concentration of 0.05 mg/kg showed a reduced alveolar bone resorption with no significant improvement with regard to the clinical status except for the reduction in pocket depth.^[27,28] On the other hand, some authors observed an increased periodontal destruction and inflammation when high doses of BPs were administered in the test group.^[29] The explanation might be that high doses of BPs stimulate the local release of pro-inflammatory cytokines such as IL-1b and IL-6 in the periodontal tissues and hence prevent the periodontal wound healing process.^[30] It has also been suggested that alendronate could reduce the collagen production and thus, by this process, block the reconstitution of the extracellular matrix of injured periodontal tissues.

Topical administration

Human Studies

With regard to human trials the existing literature demonstrate a further benefit of the systemic administration of BPs in addition to mechanical debridement compared with mechanical debridement alone. This benefit is mainly the reduction of alveolar bone loss and the preservation of the alveolar bone height. On the subject of the clinical parameters, some trials failed to show a significant improvement^[31] whereas other studies reported that BPs supported (in addition to inhibiting alveolar bone loss) the periodontal healing, in particular, the reduction of probing pocket depth and tooth mobility^[32,33]

Local administration

Studies have suggested a possible association between the systemic use of ALN and avascular osteonecrosis of the jaw ; therefore, limitations exist in the systemic use of ALN for the treatment of periodontal disease.^[34] Compared with a systemic regimen, local delivery may offer important benefits in terms of adverse reactions and patient compliance. Studies have demonstrated successful local application of ALN as an adjunct in periodontal therapy for reducing bone resorption following surgery.^[35,36] ALN also resulted in improved clinical and radiographic parameters when used in the treatment of Class II furcation defects and aggressive periodontitis.^[37,38]

Mucoperiosteal flap elevations in periodontal and oral surgery lead to alveolar bone resorption.^[39] The inhibition of this inevitable bone loss has been the subject of numerous studies on the rational use of local application of ALN in the surgical area. Another approach for the topical administration of BPs was the use of synthetic bone substitutes as a drug-delivery system with incorporated BPs. This approach of controlled local delivery of BPs combines the osteoconductive property of the calcium phosphate biomaterials and the osteoclast inhibitory action.^[40]

NEW INSIGHTS INTO ACTION OF BIPHOSPHONATE ACTION IN PERIODONTAL THERAPY:

In addition to the potentially useful effects of the bisphosphonates in preventing periodontitis-associated bone loss, other studies have focused on the potential effects of bisphosphonates in relation to “Regional accelerated phenomenon” (RAP). The phenomenon^[41] is a transient burst of localized remodeling activity following surgical wounding of cortical bone. It involves the recruitment of an increased number of osteoclasts and osteoblasts at the surgical site. The activation of RAP starts with accelerated resorptive activity by osteoclasts followed by the bone regeneration by osteoblasts. ALN has shown inhibition of bone resorption indeed as a result of flap elevation and attendant RAP.^[42] The study additionally gave relevant clinical significance,

implying that topical delivery of ALN along with the bone regenerative material may achieve new dimensions in periodontal regenerative therapy. This research provides a clue that bone-targeting properties of bisphosphonates can be harnessed along with regenerative materials to potentiate osseous regeneration.

Furthermore the use of biologic bone mediators in the improvement of poor quality bone potentially can help improve the success of dental implants. Meraw and Reeve's in a study in dogs demonstrated that dental implants coated with hydroxyapatite and ALN resulted in a significant increase in peri-implant bone.^[43] A 3-year follow-up study demonstrated that the oral administration of bisphosphonates (alendronate and risendronate) increased the percentage of successful implant therapies compared with control cases without being associated with osteonecrosis of the jaw.^[44] Given their antiresorptive action, it can be assumed that the topical administration of bisphosphonates in adjunct to conventional implant treatment might be beneficial for limiting the peri-implant bone resorption occurring after implant placement and loading.^[45] Bisphosphonates could therefore be used to slow down the physiological decrease in primary stability of the implants during the initial phase of osseointegration, thus improving bone fixation and reducing the implant failure rate. This might be particularly useful for immediate and early loading procedures, as it has been shown that with such

protocols, most failures occur in the first few months after implant placement.^[46]

ADVERSE EVENTS:

ALN, used mainly for the treatment of osteoporosis, has been associated with adverse events from the upper gastrointestinal tract with oesophageal and stomach ulcers^[47] acute phase response, hypocalcaemia and secondary hyperparathyroidism, musculoskeletal pain and Bone Osteo Necrosis (BON). Generally, intravenous bisphosphonates are more potent than oral bisphosphonates, and the frequency and severity of some of the bisphosphonate associated adverse events are dose and potency dependent. The rate of incidence of oral administration was observed as zero to minimal compared to the intravenous-use patients.^[48,49] In 2008, the American Dental Association stated that the BON risk to patients who received oral bisphosphonate therapy was low based on the literature.^[50] However, Sedghizadeh *et al.* recently challenged this statement by reporting that 4% of their patient population taking oral alendronate sodium presented active BON.^[51]

CONCLUSION:

Based on the present knowledge of BPs, the use of BPs in periodontal research shows a promising method of managing periodontal diseases by modifying the host response. Published studies tend to demonstrate that BPs prevent or at least reduce the alveolar bone loss. Even though animal and human studies have

shown a significant improvement in periodontal treatment outcome using BPs, there is a lack of data determining the optimal prescription concentration and formulation. The recent published data on BON could lead us to the question about the rationality of using BPs in periodontal treatment considering the risk/benefit ratio of such therapeutic treatment. Nevertheless the occurrence of BON is limited and the risk that it represents seems to be small in comparison with the overall health benefits for patients treated with BPs. In particular a favourable oral health status before BPs prescription is crucial to minimise the risk of BON.^[52] A simple way to avoid the side effects could be topical use of BPs with a drug-delivery system. This seems to be a promising therapeutic option and can inhibit post-surgical bone resorption. The

use of a biomaterial as a carrier or a controlled drug-delivery system is an innovation and part of a new generation biomaterials acquiring a functional role in addition to their principal use as osteoconductive scaffolds for bone regeneration.^[53] However, the benefit of inhibiting or slowing down the bone resorption after implantation of a biomaterial into bone could be questionable. In fact, with this approach the synthetic material will remain in contact with the bone for a longer period of time and therefore the bone-regeneration process will be slowed down. Based on this mini-review, it can be concluded that there is still a need to develop more clinical studies to support the use of BPs for the reinforcement of the periodontal therapeutic armada.

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FIGURES:

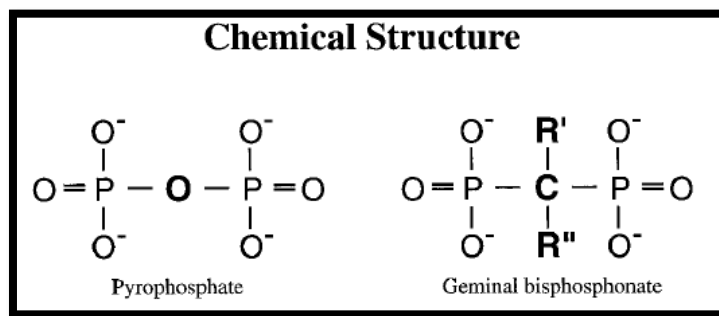


Figure 1. Chemical structure of pyrophosphate and bisphosphonates.

		Bisphosphonate	R ₁	R ₂
First Generation	—	Etidronate:	OH	CH ₃
		Clodronate:	Cl	Cl
Second Generation	—	Pamidronate:	OH	CH ₂ CH ₂ NH ₂
		Alendronate:	OH	CH ₂ CH ₂ CH ₂ NH ₂
		Tiludronate:	H	—S——Cl
Third Generation	—	Risedronate:	OH	CH ₂ —

Figure 2. Classification of bisphosphonates

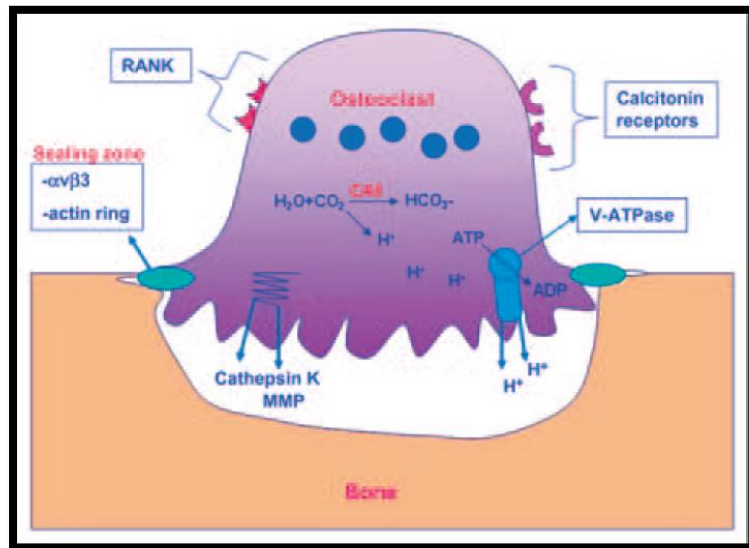


Figure 3: Mechanism of bone resorption by osteoclasts

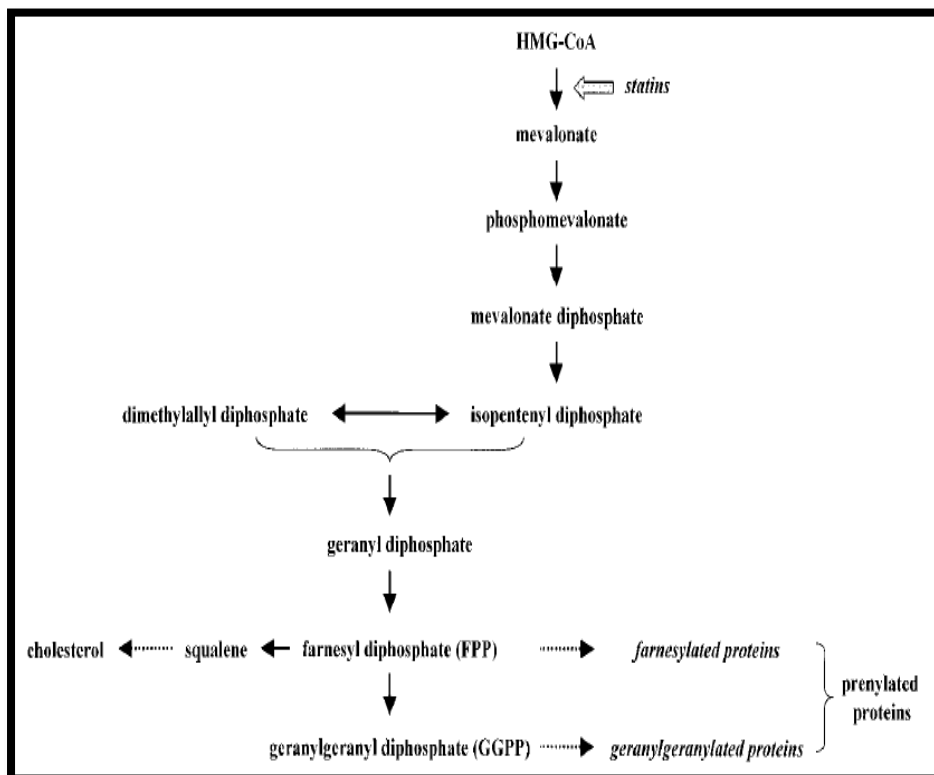


Figure 4: Schematic representation of the mevalonate pathway

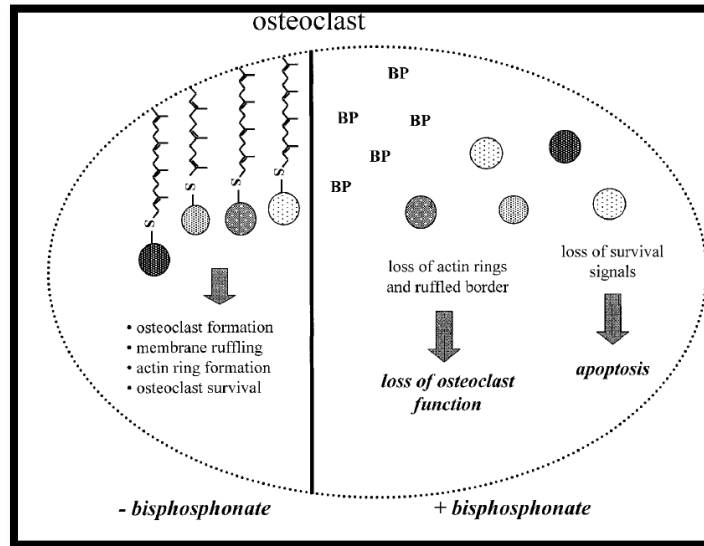


Figure 5: Cellular uptake of nitrogen containing bisphosphonates by the osteoclast leads to inhibition of the mevalonate pathway and loss of prenylated proteins, causing loss of osteoclast function and cell death by apoptosis.