Review Article

Role of Novel Adjunct Teriparatide in Periodontal Regeneration: A Current Update

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ABSTRACT

Periodontitis is a multifactorial disease that causes tooth loss. The complex pathogenesis of periodontitis implies the involvement of a susceptible host and a bacterial challenge. A number of drugs have been used as an adjunct with non-surgical periodontal therapy to treat periodontitis. Teriparatide (recombinant human parathyroid hormone [PTH]) is a bone anabolic therapy that increases bone remodeling, formation, and density; improves bone microstructure, including increased trabecular number and thickness; and reduces fracture risk. Recently some studies with Teriparatide have been done on periodontal regeneration and osseous regeneration with excellent outcome. The osteogenic potential of teriparatide opens a new door of opportunities to a periodontist to treat periodontitis effectively. This update is intended to provide an overview on the impact of teriparatide in the craniofacial skeletal, regeneration applications, and future prospects for clinical benefits of teriparatide in periodontal therapy.

Keywords: Parathyroid hormone, periodontal regeneration, teriparatide.

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Date of Submission : 01-04-2014
Reviews Completed : 15-05-2014
Date of Acceptance : 13-06-2014

INTRODUCTION

Novel strategies for periodontal disease management have been emerging as more is being learned about the role of the host response. Our ever increasing understanding of inflammation and its resolution has opened several windows for studying new periodontal treatment strategies. Non-surgical management still always remains the cornerstone of periodontal therapy. The treatment of periodontitis patients starts from a course of initial or hygiene phase, as it is beneficial for all sites.[1] For short as well as long term, success of subsequent surgical procedures depends on the standard of home care.[2]

The major component of soft and hard tissue destruction associated with periodontal disease is the result of activation of the host's immuno-inflammatory response to the bacterial challenge. The underlying biological mechanisms of this response are characterized by the expression of endothelial host-derived inflammatory mediators including cytokines and lipids by neutrophils, monocytes, lymphocytes and fibroblasts.[3] Page *et al*.[4] in 1999 reported that periodontal disease is characterized by high concentrations of MMPs, cytokines, and prostanoids in the periodontal tissue. The purpose of host modulation therapy is to restore the balance of pro-inflammatory or destructive mediators and anti-inflammatory or protective mediators to that seen in healthy individuals.

Over the past two decades, a variety of pharmacological agents have been studied for their possible roles as host modulators in the management of periodontal disease. Three categories of host-modulating agents have been investigated in the periodontal therapy: antiproteinases (which are represented by tetracyclines); anti-inflammatory drugs (Non-steroidal anti-inflammatory drugs, Statins, omega 3 fatty acids);and bone-sparing drugs (which are represented by antiresorptive agents such as bisphosphonates).[5] Recently, a fourth category has been postulated, namely, the 'bone-forming drugs', which includes teriparatide.[6] Teriparatide or rPTH (recombinant human parathyroid hormone) is a biosynthetic human parathyroid hormone, which consists of the first 34 amino acids of parathyroid hormone. This update is intended to provide an overview on the impact of teriparatide in the craniofacial skeletal, regeneration applications especially in periodontal regeneration, and future prospects for clinical benefits of teriparatide therapy.

METHODS

Dental literature was searched with Medline/ PubMed Central/Google for "teriparatide" term was searched in PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) which was further filtered for "teriparatide in dentistry", "teriparatide in dental", "teriparatide in oral medicine", "teriparatide in periodontics", "teriparatide in osteoporosis" and abstracts of all relevant papers were scrutinized thoroughly and in the end articles pertaining to the topic were included. Relevant literature for "teriparatide" in common textbooks on periodontology, oral implantology, oral medicine; bibliographies of papers and review articles together with appropriate peer reviewed journals were also scrutinized for additional information.

REVIEW OF LITERATURE

It has been known since 1932, that parathyroid hormone has anabolic effects on bone.[7] Recently, interests in its clinical application have emerged for bone regeneration in localized osseous defects and fractures.[8-11] Animal models and gene ablation models support the impact of PTH on bone development and remodeling in the craniofacial region, thus providing a sound rationale for the use of PTH for applications in oral and maxillofacial bone regeneration.[12-14] Preliminary clinical studies have shown promising results with teriparatide for periodontal regeneration and the treatment of osteonecrosis of the jaw related to the use of bone antiresorptive drugs.[15-18]

Mode of Action: Teriparatide and PTH mediate their biological effects via specific, G-protein-dependent, high-affinity membrane cell-surface receptors. These receptors are expressed on osteoblasts and renal tubular cells; both these molecules bind to the receptors with the same affinity and exert the same physiological effects on bone and kidney. Binding of ligand induces a cascade that activates protein kinase-1, cyclic adenosine monophosphate, protein kinase-C and phospholipase-C, which results into an increase in the number of active osteoblasts, a decrease in osteoblast apoptosis and probably, recruitment of bone lining cells as newly formed osteoblasts, thereby increasing bone strength, mass and diameter, and bone structural integrity, as well as increasing serum and urinary levels of markers of bone formation and resorption.[6]

Indications: Teriparatide has been reported to be beneficial in the management of following conditions: Osteoporosis,[19,20] bisphosphonate-related osteonecrosis of the jaw,[21,22] osteogenesis imperfecta,[23] osteoarthritis,[24] and fracture repair.[25]

Clinical studies of Teriparatide in periodontal regeneration (Table-1):

Jung *et al*.[26] in 2007 analyzed the effect of matrix bound parathyroid hormone on bone regeneration and found significant new bone formation but there was no more bone to implant contact. In a study conducted by Moore *et al*.[27] to evaluate the osteogenic potential of Teriparatide on various parts of human skeleton, mandible was found to have maximum activity rate. Bashutski *et al*.[11] evaluated the effect of Teriparatide on periodontal regeneration in patients with severe periodontitis. They used 20µg dose along with calcium and vitamin D supplement daily for six weeks and found significant improvement in clinical and radiographic outcomes. Similarly, Yun *et al*.[28] administered PTH systemically in a rat model and found stimulated local bone formation, whereas a local delivery of PTH by using β-tricalcium phosphate was not as much effective like systemic delivered PTH. Valderrama *et al*.,[14]valuated role of parathyroid hormone bound to a synthetic matrix in guided bone regeneration around dental implants placed in dog's mandible and found that covalently bound PTH to a synthetic, RGD (arginine-glycine-aspartic acid) -modified Poly Ethylene Glycol hydrogel marginally results into improved bone formation at 2 weeks of healing compared to the use of PEG alone.

Kuchler *et al*.[29] investigated the effects of teriparatide on the osseointegration of titanium implants in 24 individuals and reported higher median values of NBV/TV (new bone-volume-per-tissue-volume (NBV/TV) and NBIC (new bone-to-implant-contact) in teriparatide groups in comparison to control group. This was the first histological

Table 1: Studies pertaining to clinical implications of Teriparatide in periodontal regeneration:

Year	Author	Study
2007	Jung *et al*.[26]	The effect of matrix bound parathyroid hormone on bone regeneration. (Animal study)
2010	Moore *et al*.[27]	Assessment of regional changes in skeletal metabolism following 3 and 18 months of teriparatide treatment. (Human Study)
2010	Bashutski *et al*.[11]	Teriparatide and Osseous Regeneration in the Oral Cavity. (Animal study).
2010	Yun *et al*.[28]	Effect of systemic parathyroid hormone (1-34) and a beta-tricalcium phosphate biomaterial on local bone formation in a critical-size rat calvarial defect model. (Animal Study).
2010	Valderrama *et al*.[14]	Evaluation of parathyroid hormone bound to a synthetic matrix for guided bone regeneration around dental implants: a histomorphometric study in dogs. (Animal study).
2011	Kuchler *et al*.[29]	Short-term teriparatide delivery and osseointegration: a clinical feasibility study. (Human Study).
2012	Bashutski *et al*.[30]	Systemic Teriparatide Administration Promotes Osseous Regeneration of an Intrabony Defect: A Case Report. (Human Study).
2012	Takedachi *et al*.[31]	Present status of periodontal regeneration - FGF-2 and Teriparatide. (Animal study).

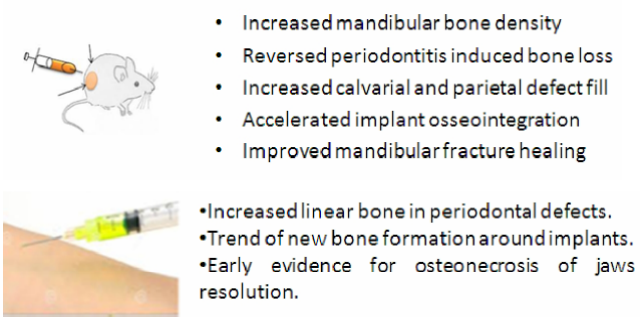

Figure1: Impact of PTH 1-34 on the craniofacial skeleton in rodents and human.[18]

data on the osseointegration of titanium study implants in individuals treated with teriparatide.

In another case report, Bashutski *et al.*[30] studied the effect of teriparatide on periodontal bone regeneration. They administered teriparatide in conjunction with traditional open-flap debridement surgery and found that teriparatide offers potential for the regeneration of bone in severe intrabony defects resulting from chronic periodontitis. In a recent clinical trial, Takedachi *et al.*[31] discussed about the present status of periodontal regeneration and concluded that FGF-2 and teriparatide both has stimulatory effect on bone regeneration and may be helpful in future.

Biological response marker during teriparatide therapy: Change in bone mineral density (BMD) is one of the best responses seen after teriparatide therapy. Changes often require a minimum of one year to observe measureable changes. Monitoring with a marker such as procollagen type-I N propeptide (PINP), an osteoblast-derived protein, during teriparatide treatment may provide clinically useful information for managing patients with osteoporosis. PINP monitoring may provide information supplemental to BMD monitoring and be a useful aid in managing patients receiving anabolic osteoporosis treatment in the same way that biochemical markers of bone resorption are useful in monitoring antiresorptive therapy.[32]

Adverse effect of teriparatide therapy: PTH (teriparatide) has been used in the treatment of osteoporosis extensively, and can sometimes cause transient hypercalcemia, but to date there have been no reports of persistent hypercalcemia and hypophosphatemia resulting from its use.[33] A "black box" warning is associated with use of teriparatide that is the occurrence of osteosarcomas.[34] Teriparatide should also not be administered to patients with primary or any form of secondary untreated or unresolved hyperparathyroidism.[18]

Mode of Administration: Currently, teriparatide is administered systemically, but has drawbacks that include the requirement for self-injection and exposure of drug to non-targeted sites—rendering it less than ideal for enhancing localized bone regeneration. A local therapy has many potential advantages, such as less adverse side-effects resulting from systematic administration, decreasing dose or number of dosages, and maintaining local agent levels within a desirable range.

Wei *et al.*[35] formulated the Poly (lactic-co-glycolic acid) (PLGA) microspheres to carry and control the release of PTH. Subsequently Liu *et al.*[36] developed, a biodegradable polymer, poly (l-lactic acid) (PLLA)-based implantable delivery system containing alternative layers of polyanhydride isolation layers and PTH-loaded alginate layers which demonstrated released PTH to be biologically active and holds promise for both systemic and local therapies.

DISCUSSION & CONCLUSIONS

Primary goal of using teriparatide for craniofacial defects or periodontal regeneration is to enhance healing. So in such condition the timing for the application of teriparatide in relation to the stages of bone healing becomes critical. A current concept in the mechanism of teriparatide action is related to its effect to stimulate processes associated with bone formation before it stimulates processes associated with bone resorption. This sequence of events has led to the concept of the anabolic window; the period of time when teriparatide is maximally anabolic.[37-38]

Optimal duration for teriparatide therapy needs further exploration. The most reasonable answer to this is probably not beyond six months because the normal bone healing time range is around six months. However, the treatment time should be short to minimize the adverse effects like hypophosphatemia, hypercalcemia or more extent to osteosarcoma. In some clinical studies the duration ranged from 4 to 8 weeks.[10,11,28]

Next future requisite is to standardize the form of application of teriparatide in periodontal regeneration. The drug delivery mode should be non-invasive, reliable, easy to use and comfortable to both patients as well as to the operator. Although, Wei *et al.*[35] and Liu *et al.*[36] have tried to develop local delivery form of teriparatide and found positive results too, but in contrast, Yun *et al.*[28] didn't found local delivery form as superior like systemic form. Therefore, more clinical studies are required to formulate a more effective form of teriparatide which is noninvasive as well as cost effective too. So for periodontal regeneration there is a clear need for improved therapeutics which can target localized osseous healing as desired. Moreover as Moore *et al.*[27] has reported more activity of bone formation in mandible with the teriparatide therapy, which is advantageous for the future implant and periodontal surgery.

With the introduction of teriparatide i.e. anabolic drug in a periodontist armory, a new door of periodontal regeneration has been opened. Its use as an adjunct to traditional gold standard non-surgical periodontal therapy seems to be a novel therapeutic approach. There are numerous concerns

about the safety, efficacy, optimal dosage and drug delivery approaches, so large scale clinical studies are required to eliminate such concerns and to facilitate the use of Teriparatide in periodontal regeneration.

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