Review Article

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Teriparatide: A Novel Means to Ultimately Achieve True Regeneration!!!

Dentistry Section

HARPREET SINGH GROVER[1], SHAILLY LUTHRA[2], SHRUTI MAROO[3]

ABSTRACT

"Perioceutics" or the use of the pharmacological agents which are specifically developed to manage periodontitis, is an interesting and an emerging aid in the management of periodontal diseases, along with mechanical debridement. Host modulation therapies are being proposed and developed to bring down excessive levels of enzymes, cytokines, prostanoids, as well modulate osteoclast functions. Over the past two decades, many drugs have been investigated for their host modulating properties in both animal and early human clinical studies. These agents include non-steroidal anti-inflammatory drugs, sub antimicrobial dose doxycycline and systemic bisphosphonates. Recently, a new drug has been added to the list, namely, teriparatide, which is a bone forming drug. It is a biosynthetic human parathyroid hormone. Multiple clinical trials have shown that teriparatide is associated with increased bone mineral density. This review has focused on the mechanism of action of teriparatide and its potential role in the treatment of periodontal disease.

Key words: Anabolic agent, Bone, Host modulation, Parathyroid hormone, Periodontitis, Teriparatide

The primary aetiology of periodontal diseases and chronic inflammation around dental implants is a bacterial infection [1]. In essence, a gram negative infection is necessary, but not sufficient to induce periodontal disease initiation or progression. Ultimately, it is the host's reaction to the presence of the bacteria that mediates tissue destruction. Therefore, it is logical to consider therapeutic approaches that manipulate the host response, in addition to antibacterial approaches in the management of periodontitis and peri-implant disease.

This concept of host response modulation was introduced to dentistry by Williams and Golub [2]. Williams, in 1990, concluded that, "There are compelling data from animal and human trials which indicate that pharmacologic agents that modulate the host responses and are believed to be involved in the pathogenesis of periodontal destruction may be effective in slowing progression of periodontal disease" [3].

Various Host Modulatory Therapies (HMT) have been developed or proposed, with the goal of reducing tissue destruction and stabilizing or even regenerating the periodontium, by modifying or downregulating destructive aspects of host response and upregulating protective or regenerative responses.

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 [4]:

1. Antiproteinases (which are represented by tetracyclines),
2. Anti-inflammatory drugs (Non-steroidal anti-inflammatory drugs, Statins, omega 3 fatty acids) and
3. Bone-sparing drugs (which are represented by antiresorptive agents such as bisphosphonates).

Recently, a fourth category has been postulated, namely, the 'bone-forming drugs', which includes teriparatide.

Teriparatide (Forsteo® or ForteoA®, Eli Lilly), a biosynthetic human parathyroid hormone, which consists of the first 34 amino acids of parathyroid hormone, is an anabolic agent. It has been known since 1932, that parathyroid hormone has anabolic effects on bone [5], but interest in its action lay dormant for almost 50 years until synthetic manufacturing of parathyroid hormone became possible in 1974. Multiple clinical trials have shown that teriparatide is associated with increased Bone Mineral Density (BMD). This review has focused on the mechanism of action of teriparatide and its potential role in periodontal regeneration.

Mechanism of Action

Endogenous Parathyroid Hormone (PTH), an 84-amino acid peptide, plays a central role in calcium and phosphate metabolism in the bone and kidney. Its physiological effects include stimulation of bone formation by directly affecting bone-forming cells (osteoblasts) and increasing renal tubular re-absorption of calcium and excretion of phosphate, and by indirectly increasing intestinal absorption of calcium via its effects on 1,25-dihydroxyvitamin D production [6].

Teriparatide and PTH mediate their biological effects via specific, G-protein-dependent, high-affinity membrane cell-surface receptors which 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. It has been suggested that ligand binding induces a cascade that activates protein kinase-1, cyclic adenosine monophosphate, protein kinase C and phospholipase C. The activation of these pathways results in 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].

Other factors may also play a role in the anabolic effect of teriparatide. Basic fibroblast growth factor 2 (bFGF-2) is also up-regulated in teriparatide treated individuals [7]. Since bFGF-2 regulates the proliferation and differentiation of osteoblast progenitors, this cytokine could play an important role in the bone formative response to teriparatide therapy [8]. Also, the osteocytic Sclerostin (SOST) gene may be transcriptionally suppressed by PTH. As a result, reductions in sclerostin, a potent inhibitor of bone formation, could account for part of the anabolic response to PTH [9].

Continuous vs. Intermittent Debate

It has now been widely accepted that intermittent teriparatide is anabolic and that continuous endogenous PTH is catabolic. Although several mechanisms have been postulated for this observation, the exact mechanisms for these differential effects

remain incompletely understood. Intermittent and low dosages of PTH, such as those which are achieved with a daily subcutaneous teriparatide administration, are believed to form, what has been termed as an 'anabolic window', a time during which bone formation is stimulated before a secondary increase in bone resorption occurs, resulting in an overall anabolic period [10]. In contrast, a continuous PTH infusion leads to a persistently and a markedly enhanced bone resorption and suppression of bone formation which results from its discordant effects on $1,25(OH)_2$ vitamin D, increased receptor activator of nuclear factor kappa-B ligand (RANKL) and decrease in osteoprotegerin (OPG) expression [10].

The effect of an intermittent teriparatide treatment not only increases trabecular thickness, but it also increases trabecular connectivity, as was verified by microcomputer tomography of transiliac bone biopsies [11].

Pharmacokinetic Properties

The bioavailability of teriparatide is approximately 95% after its subcutaneous administration. Maximum serum levels are achieved after approximately 30 min and its half-life is approximately 75 min as compared to a half-life of approximately 10 min. after an intravenous administration. Its serum levels are 20-30% lower in men as compared to those in women after the administration of subcutaneous injections. Teriparatide is metabolized in the liver and kidneys [12].

Outcomes of Various Preclinical Studies

Teriparatide increases the structural integrity of trabecular bone (Shen et al., 1993) [13] and it increases bone strength. (Mosekilde et al., 1991) [14]. The anabolic effects are pronounced in the trabecular bone and on the endosteal surface of cortical bone. In rat, cortical bone mass and strength are increased (Ejersted et al. 1993; Oxlund et al., 1993) [15,16]. In some species such as rat, little remodelling of cortical bone is seen. In contrast, a remodelling does occur in species such as monkeys, dogs, and rabbits and in these species, parathyroid hormone treatment increases cortical bone porosity, however, due to the concomitant increase in bone diameter (i.e. an anabolic effect on the periosteal surface), bone strength seems to be unaffected by the increased porosity (Mashiba et al., 2001) [17].

With the help of tissue engineering, teriparatide has been fused with various biomaterials like polyethylene glycol that are used to enhance bone generation and implant osseintegration. A study which was carried out on the acute defects which were created around dental implants in dogs at 2 weeks of healing, to evaluate the effect of PTH 1-34 which was covalently bound with a synthetic Polyethylene Glycol-based hydrogel, showed promising results [18].

Also, experimental studies which were done on rats have shown that teriparatide accelerates tooth movement during orthodontic tooth movements, by causing a three-fold increase in osteoclast number on the compression side and causing bone deposition on the tension side (Soma et al., 1999) [19]. But previous studies do not support the use of this drug in orthodontic treatment, as no osteoclast mediated bone resorption was seen to produce any impact on tooth movement. (Schmidt et al., 1995) [20].

Clinical Studies

Bashutski et al., in 2010, conducted a study to evaluate the effect of daily administration of teriparatide in conjuction with oral surgical procedures, on periodontal regeneration in men and women with severe periodontal disease. A total of 40 patients with severe periodontitis underwent periodontal surgeries and they received daily injections of teriparatide (20 µg) or placebo, along with calcium and vitamin D supplementation for a 6 week period. Significantly improved clinical and radiographic outcomes were achieved in patients who received teriparatide [21].

Another case which was reported by Bashutski in 2012, demonstrated that teriparatide administration, in conjunction with periodontal surgery, resulted in improved clinical and radiographic outcomes that were sustained for 4 years [22]. Another recent study assessed the osteogenic effect of teriparatide on various parts of the human skeleton and found that the mandible had one of the highest activity rates [23]. This may suggest as to why a systemic teriparatide administration resulted in such a high clinical success when it was used as an adjunct to an oral surgical procedure. Additionally, this suggests that the oral cavity may be one of the most receptive sites in the body to develop a response to teriparatide .

In conformation with the 'anabolic window', results from clinical trials showed that after commencing treatment with teriparatide, markers of bone formation were significantly increased sooner (from 1 month) than markers of bone resorption (from month 3) [24], thus indicating overall bone remodeling, with the net balance in favour of bone formation [25].

Other clinical trial which was conducted by using teriparatide at doses of 20 µg or 40 µg showed statistically significant results which were associated with the improved quality of non-vertebral cortical bone and improved geometry and distribution of the trabeculae within the bone. However, the effect of PTH on effective bone remodeling and stimulation of osteoblasts gradually wanes between 18 to 24 months, thus suggesting an ideal course of treatment at around 6-12 months [26].

Comparison with Other Drugs

Teriparatide (40µg/day i.e., a dosage which is higher than the approved dose) was compared head to head with alendronate (10mg/day) in a randomized, double blind trial. After 14 months of treatment, the increase in BMD, which was significantly higher in the teriparatide group, was more effective than alendronate in increasing bone formation marker levels from baseline (Body et al., 2002) [27]. The higher rates of bone formation and resorption may be attributed to a large number of multicellular unit forming new bones, whereas alendronate therapy reduces both bone formation and resorption, thereby preserving the bone [28].

Hwang et al., compared teriparatide with calcitonin and concluded that BMD was significantly greater in patients who took teriparatide [29]. Similar outcomes were obtained in various other studies (Kung et al.,) [30].

Recker et al., compared the effects of 20µg/daily teriparatide and 2gm strontum ranelate on Procollagen type I N-terminal propeptide (PINP), a serum biomarker of bone formation. PINP levels increased significantly in the teriparatide group at 1 month and they increased till 6 months [31].

Sequential and Combined Treatment

Loss of bone mass which was gained during teriparatide treatment is the principal concern, following cessation of anabolic therapy. Teriparatide treatment is time restricted due to concerns which are related to osteosarcoma risk. Studies suggest that the bone loss which results after teriparatide cessation can be attenuated with antiresorptive treatment [32]. Patients who received at least 24 months of treatment with bisphosphonates during the 30 month post-teriparatide phase of the Fracture Prevention Trial, demonstrated further increases in BMD. In contrast, those who did not receive anti-resorptive treatment during the 30 month post-teriparatide treatment phase, demonstrated a reduction in BMD, that was not different from placebo ($P < 0.05$) [33]. Similar improvements in BMD were demonstrated in 2 studies which were done by using teriparatide, followed by raloxifene as compared to those which were done by using teriparatide, followed by placebo [34,35].

Adverse Effects

The FDA has issued a black-box warning because of the drug's

association with an increased incidence of osteosarcoma (a malignant bone tumour) in male and female rats. The effect was dependent on the dose and treatment durations and it was observed at systemic exposures to teriperatide which ranged from three to 60 times the exposure in humans who were given a 20-micro grams dose [36]. It should not be prescribed for patients who are at an increased risk for osteosarcoma at baseline, including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, or a previous radiation therapy which involved the skeleton.

Adverse drug events (ADEs) which are associated with teriparatide use include—but are not limited to—headache, asthenia, neck pain, hypertension, angina pectoris, syncope, nausea, constipation, dizziness, depression, insomnia, vertigo, hyperuricaemia, and hypercalcaemia. ADEs appear to increase with higher dosages.

According to the study of Body et al., significantly fewer patients who took teriparatide (5.5%) had a new or worsened back pain as compared to patients who took alendronate (19.2%), although six patients who took teriparatide and none who took alendronate reported leg cramps. In this study, 28 women who took teriparatide and two who received alendronate had elevated four-hour to six-hour post-dose serum calcium levels at least once, and one woman discontinued teriparatide treatment because of an increase in her serum calcium levels after taking the injection. The women with elevated serum calcium levels were asymptomatic, and these increases were not associated with clinically significant adverse outcomes [27].

Future Prospects

Periodontitis is a localized disease as compared to osteoporosis, and so, future strategies which are undertaken to optimize teriparatide administration could include local concentration at sites of osseous wound healing, to maximize benefits and to minimize systemic effects. However, it is challenging to develop a local delivery system that is able to deliver teriparatide at low and intermittent doses, which is what is required to achieve anabolic effects. Several local delivery systems have been developed already and they have been tested in preclinical animal models, with varying rates of success. In foxhounds, an arginine–glycine–aspartic acid modified polyethylene glycol-based matrix which contained covalently bound peptides of PTH, resulted in significantly more new bone formation but not more bone-to-implant contact after 4 and 12 weeks [37]. In contrast, a systemic PTH administration in a rat model was found to stimulate local bone formation, whereas a local delivery of PTH by using β-tricalcium phosphate did not [38]. There is a clear need for improved therapeutics that can target localized osseous healing as desired, to get periodontal regenerative outcomes.

CONCLUSION

The introduction of these anabolic agents has widened our treatment armamentarium in the management of periodontitis. Using systemic teriparatide as an adjunct to a periodontal surgery may project it as a promising host modulating agent, to promote osseous regeneration with long-term results. However, future large-scale clinical trials are needed in humans, to fine tune the indications and to answer questions which are related to safety, efficacy, optimum dosing and feasibility of local drug delivery systems and their optimum durations of use. Clarification of these important aspects could further improve the effectiveness of this drug.

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PARTICULARS OF CONTRIBUTORS:
1. Professor and Head, Department of Periodontics & Oral Implantology SGT Dental College, Hospital and Research Institute, Gurgaon, Haryana., India.
2. Resident, Department of Periodontics & Oral Implantology SGT Dental College, Hospital and Research Institute, Gurgaon. Has A Post Graduate Certificate in Implantology & Oral Rehabilitation from New York University, College Of Dentistry, USA.
3. Resident, Department of Periodontics & Oral Implantology SGT Dental College, Hospital and Research Institute, Gurgaon, Haryana.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Shailly Luthra,
1004, Antariksh Greens, Plot No. 8, Sector-45, Gurgaon, Haryana, India.
Phone: 08800235100, 09654969330
E-mail: shaillyluthra@gmail.com

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