Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 1116-1121 | ISSN:2251-6727

Alveolar Bone Regeneration- The Clinician's Perspective!

Dr. Grishmi Niswade[1]

1. Reader, Department of Periodontology, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Nagpur

Corresponding author-

Dr. Grishmi Niswade, Swargiya Dadasaheb Kalmegh Smruti Dental College and Hospital, Nagpur

(Received: 16 September 2024 Revised: 11 October 2024 Accepted: 04 November 2024)

KEYWORDS

teriparatide, alveolar bone, regeneration, parathyroid hormone

ABSTRACT:

Periodontal disease is a chronic inflammatory disease affecting the supporting structures of the periodontium. This disease has a high global prevalence eventually affecting the quality of life of the individual due to tooth loss. The etiopathogenesis and pathology of periodontal disease is an ever-evolving research area in the field of periodontology. Newer treatment modalities have emerged that can be given to patients in addition to non-surgical and surgical periodontal therapy, which will remain the cornerstone of treatment for periodontal disease. The host immune inflammatory response contributes to the loss of periodontal support. Hence, alternative treatment modes targeting the host response can improve the outcome of periodontal treatment. Teriparatide is one such anabolic drug which is a recombinant form of parathyroid hormone. It has been used widely for treating osteoporosis but also has promising results in dentistry. This review focuses on the update of teriparatide and its periodontal applications for bone regeneration.

Introduction

Periodontitis is a chronic inflammatory disease of the supporting tissues caused due to dental plaque.[1] The periodontal pathogens present in the dental plaque react with host immune cells and lead to a cascade of release of pro-inflammatory mediators which leads to further clinical attachment loss, bone loss and eventually tooth loss. The resultant bone loss due to this process is caused by upregulation of bone resorptive pathways and downregulation of bone formative pathways.[2] Therefore, predictable periodontal treatment procedures that can achieve periodontal regeneration are required. Teriparatide is one such systemic anabolic drug that can be used for bone regeneration. Teriparatide is approved by the Food and Drug administration in 2002 for the treatment of osteoporosis. Literature shows that administration of teriparatide is osteoporosis patients results in enhanced bone mineral density and decreased risk of fractures. This shows that teriparatide can be used as host modulating agent in the treatment of osseous defects seen in periodontitis.[3]

Teriparatide

It is a osteoanabolic recombinant fragment of human parathyroid hormone (PTH) consisting of first amino (N)- terminal 34 amino acids. It was largely used for dealing with osteoporosis in post-menopausal women with high risk of fracture. The additional indications include in men with primary or hypogonadal osteoporosis with high risk of fracture and for the treatment of glucorticoid induced osteoporosis with high risk of fracture in men and women. Apart from these approved indications for the use of teriparatide, research is in progress for the use of teriparatide in treatment of fracture healing, hypoparathyroidism, osteonecrosis of jaw and periodontal disease.

The currently approved dosage of teriparatide for the treatment of osteoporosis is 20 mcg via subcutaneous injection in the abdominal wall or anterior thigh for a maximum of 2 years due to the risk of osteoscarcoma. Prefilled pens containing 20 mcg teriparatide for a 28 day regimen are available in the market. Brand names of teriparatide available in India in injection form are

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 1116-1121 | ISSN:2251-6727

Gemtide, Forteo, Terifrac, Zotide, Bonista, Tricium PTH injection, Bonmax, Nu PTH, Gemfrac etc. Following the regimen of Teriparatide in a patient with osteoporosis, an anti-resorptive drugs such as bisphosphonates are given to preserve the increase in bone mineral density achieved by teriparatide. Bisphosphonates are related to oral complications such as bisphosphonate related osteonecrosis of jaw (BRONJ) which is characterised by necrosis of alveolar bone that does not heal for 8 weeks in an individual taking bisphosphonate therapy. [3-5]

Mechanism of Action

Excess PTH causes osteoclast activation and bone resorption. The dose and pattern of exposure to bone decides the effect of PTH on bone. Intermittent low dose administration of PTH has bone formative effects whereas continuous high dose administration has bone resorptive effects.

Teriparatide has anabolic as well as catabolic mode of action through its action on PTH type 1 receptors which are present on cell surfaces of osteoblasts, osteocytes and renal tubular cells. This binding leads to Gs mediated activation of adenylate cyclase and Gq mediated activation of protein kinase C (PKC). Adenylate cyclase catalyses the conversion of cAMP to Protein kinase A (PKA). Activation of PKA pathway acts as a pathway for the catabolic and anabolic action of PTH.

The effect of teriparatide on calcium and phosphate homeostasis are increase in serum calcium and decrease in serum phosphate through its effect on kidney and bone. Increase in serum calcium is achieved by mobilization of calcium from the bones into the circulation and increased distal tubular reabsorption of calcium in the kidneys. Decrease in serum phosphate is achieved by inhibition of proximal tubular reabsorption of phosphate. [3-5]

Indications

- Treatment of osteoporosis in postmenopausal women with a high risk for fracture
- Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
- Treatment of men and women with systemic glucocorticoid-induced osteoporosis at high risk for fracture

Contraindications

- Hypersensitivity to teriparatide or its excipients.
- Increased basal risk for osteosarcoma like Paget disease of bone, history of primary or secondary skeletal malignancy, history of ionizing radiation involving the skeleton, paediatric and young patients with open epiphyses
- Hypercalcemia
- Hypercalciuria and/or urolithiasis because it causes hypercalciuria, which promotes urinary stones.

Administration

Dosage- subcutaneous injection in the abdomen or anterior thigh of pens filled with 20 micrograms per day for a maximum of 2 years because of the risk of developing osteosarcoma.

Adverse effects

- Nausea, headache, dizziness, orthostatic hypotension
- Hypercalcemia, hypercalciuria
- Osteoscarcoma when taken in relatively high doses ranging from 5 to 75 mcg/kg/day for a period of 2 years. This finding is based on a study conducted on Fisher rats which were subjected to this dosage and duration of teriparatide administration. This adverse effect is considered minimal and not significant for humans because of the difference in bone physiology of rats and humans, 2 years is almost 90% of lifespan of rats as compared to 2 years being 2-3% of lifespan of humans and the dose being 3 to 58 fold high as being used in humans. Therefore the risk of developing osteoscaroma in humans is very less as suggested by a study with 8 year analysis of effect of teriparatide administration in humans. [3-5]

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 1116-1121 | ISSN:2251-6727

Literature for use of teriparatide in periodontal therapy and medical therapy

As teriparatide is well established for its effect on bone for preventing fractures in severe cases of osteoporosis, it can be a potential host modulating agent used for the treatment of periodontitis.

Ebrahimi S et al 2022[6] conducted a clinical trial to evaluate the effects of teriparatide (CinnoPar) on healing and postoperative complications in mandibular bone fractures. The author concluded that within the limitations of the study it seems that in mandibular fractures, teriparatide did not affect bone fusion or postoperative complications, so its use is not recommended for better bone fusion and fewer postoperative complications of mandibular fracture during the first month.

Sim et al 2020[7] conducted a clinical trial to evaluate the effect of teriparatide on Medication-related osteonecrosis of the jaw (MRONJ). In this double-blind, randomized, controlled trial, 34 participants with established MRONJ, with a total of 47 distinct MRONJ lesions, were allocated to either 8 weeks of subcutaneous teriparatide (20 mg/day) or placebo injections, in addition to calcium and vitamin D supplementation and standard clinical care and participants were observed for 12 months.

Kahekashi et al 2015[8] reported the outcomes of daily teriparatide injections for the treatment of bisphosphonate-related osteonecrosis of the jaw in 10 patients. The study found that administration of teriparatide in patients with osteonecrosis of the jaw promotes bone formation and subsequent sequestration over a short period of time. These results suggest that adjunctive teriparatide therapy is a viable and effective option for treating osteonecrosis of the jaw.

Bashutski in 2012[9], demonstrated in a case report that open-flap debridement surgery in conjunction with daily systemic administration of 20 µg teriparatide, oral vitamin D, and calcium supplements for 6 weeks, resulted in improved clinical and radiographic outcomes that were sustained for 4 years.

Aggarwal P et al 2012[10] conducted a 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.

Takedachi et al 2012[11] discussed about the present status of periodontal regeneration in periodontitis patients and concluded that FGF-2 in the form of topical application and teriparatide as subcutaneous administration both has stimulatory effect on bone regeneration and may be helpful in future.

Bashutski et al 2011[12] assessed the outcomes of periodontal surgery and teriparatide administration in vitamin D sufficient and insufficient individuals. The study suggested that radiographic outcomes were better in vitamin D sufficient patients taking teriparatide suggesting that teriparatide benefits from vitamin D sufficient patients taking teriparatide to promote oral bone formation. However, vitamin D deficient individuals benefit minimally from periodontal surgery.

Kuchler et al 2011[13] conducted a study in 24 individuals with edentulous lower jaws. All participants received 2 study implants to support overdentures and 2 additional mini implants placed during the surgery in the mandible which were then randomly assigned to receive 20 µg of teriparatide once daily for 28 days or no treatment. Favorable outcomes were observed in the PTH group.

Bashutski et al 2010[14] conducted a study to evaluate the effect of daily administration of teriparatide, in conjunction with an oral surgical procedure, on periodontal regeneration in men and women with severe periodontal disease. A total of 40 patients with severe, stage III periodontitis underwent periodontal surgery and received daily injections of teriparatide (20 µg) or placebo, along with oral calcium (1000 mg) and vitamin D (800 IU) supplementation, for 6 weeks. The patients were followed for 1 year. The primary outcome was a radiographic linear measurement of alveolar bone level. Secondary outcomes included clinical variables, bone turnover markers in serum and oral fluid, systemic bone mineral density, and quality of life. Significantly improved clinical and radiographic outcomes were achieved in patients who received teriparatide.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 1116-1121 | ISSN:2251-6727

In a study conducted by Moore et al 2010[15] to evaluate the osteogenic potential of Teriparatide on various parts of human skeleton, mandible was found to have maximum activity rate. 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.

Miyauchi et al 2010[16] assessed the safety and efficacy of teriparatide 20 microg/day in Japanese men and women with osteoporosis at high risk of fracture. The study showed that teriparatide 20 microg/day was well tolerated and stimulated bone formation in Japanese subjects with osteoporosis at high risk of fracture during 18 and 24 months of treatment.

Lindsay et al 2009[17] evaluated the effect of teriparatide in post-menopausal osteoporotic women. Postmenopausal women with osteoporosis were randomized to once-daily subcutaneous injection with placebo, teriparatide 20 µg, or teriparatide 40 µg plus calcium and vitamin D supplementation. This study suggests that increased nonvertebral fracture protection, reduced back pain, and reduced occurrence of side effects with longer duration of teriparatide therapy.

Recker et al 2009[18], 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.

Hwang et al 2006[19], compared daily subcutaneous injections of teriparatide with calcitonin in post-menopausal osteoporotic women and concluded that BMD was significantly greater in patients who took teriparatide.

In conformation with the ‘anabolic window’, results from clinical trial conducted by Deal C et al 2005[20] 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), thus indicating overall bone remodeling, with the net balance in favor of bone formation.

Gallagher C et al 2005[21] evaluated the relationship between prior fractures and risk of new fractures in 931 postmenopausal women with prevalent vertebral fractures randomized to daily placebo or teriparatide (20 µg). In the teriparatide-treated group, there was no significant increase in vertebral or nonvertebral fracture risk in these subgroups.

Finkelstein et al 2006[22] conducted a study to determine whether teriparatide increases osteoblast activity when the ability of teriparatide to increase osteoclast activity is suppressed by alendronate. In men receiving teriparatide monotherapy, levels of all bone turnover markers increased markedly during the first 6 months of teriparatide administration and then declined toward baseline during the next 18 months.

Conclusion

The treatment of Periodontitis requires accurate diagnosis, removal of causative factors and prevention strategies for modifying risk factors of the disease. The studies from this literature review show encouraging clinical outcomes with the use of teriparatide for bone regeneration. However, long term randomized controlled clinical trials are required to prove the precise long-term benefits of this drug in bone regeneration.

References

1. Mehrotra N, Singh S. Periodontitis. 2022 May 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 31082170.
2. Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and prevention. Int J Health Sci (Qassim). 2017 Apr-Jun;11(2):72-80. PMID: 28539867; PMCID: PMC5426403.
3. Grover HS, Luthra S, Maroo S. Teriparatide: a novel means to ultimately achieve true regeneration!!! J Clin Diagn Res. 2013 Aug;7(8):1820-3. doi: 10.7860/JCDR/2013/5893.3280. Epub 2013 Aug 1. PMID: 24086927; PMCID: PMC3782984.
4. Blick SK, Dhillon S, Keam SJ. Teriparatide: a review of its use in osteoporosis. Drugs. 2008;68(18):2709-37. doi: 10.2165/0003495-200868180-00012. PMID: 19093708.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 1116-1121 | ISSN:2251-6727

5. Cheng ML, Gupta V. Teriparatide - Indications beyond osteoporosis. Indian J Endocrinol Metab. 2012 May;16(3):343-8. doi: 10.4103/2230-8210.95661. PMID: 22629497; PMCID: PMC3354838.
6. Ebrahimi S, Navabazam A, Salemi F, Khaleghi F, Barzegar M, Saghafi F, Fallahzadeh H. The efficacy of teriparatide (Cinnopar®) on bone repair in mandibular fractures: A single blinded randomized clinical trial. J Craniomaxillofac Surg. 2022 Dec;50(12):923-928. doi: 10.1016/j.jcms.2022.12.002. Epub 2023 Jan 5. PMID: 36646571.
7. Sim IW, Borromeo GL, Tsao C, Hardiman R, Hofman MS, Papatziamos Hjelle C, Siddique M, Cook GJR, Seymour JF, Ebeling PR. Teriparatide Promotes Bone Healing in Medication-Related Osteonecrosis of the Jaw: A Placebo-Controlled, Randomized Trial. J Clin Oncol. 2020 Sep 10;38(26):2971-2980. doi: 10.1200/JCO.19.02192. Epub 2020 Jul 2. PMID: 32614699.
8. Kakehashi H, Ando T, Minamizato T, Nakatani Y, Kawasaki T, Ikeda H, Kuroshima S, Kawakami A, Asahina I. Administration of teriparatide improves the symptoms of advanced bisphosphonate-related osteonecrosis of the jaw: preliminary findings. Int J Oral Maxillofac Surg. 2015 Dec;44(12):1558-64. doi: 10.1016/j.ijom.2015.07.018. Epub 2015 Aug 21. PMID: 26304604.
9. Bashutski JD, Kinney JS, Benavides E, Maitra S, Braun TM, Giannobile WV, McCauley LK, Eber RM. Systemic Teriparatide Administration Promotes Osseous Regeneration of an Intrabony Defect: A Case Report. Clin Adv Periodontics. 2012 May;2(2):66-71. doi: 10.1902/cap.2012.110043. PMID: 26525954; PMCID: PMC4623592.Aggarwal P, Zavras A. Parathyroid hormone and its effects on dental tissues. *Oral Dis.* 2012;18:48–54.
10. Aggarwal P, Zavras A. Parathyroid hormone and its effects on dental tissues. Oral Dis. 2012;18:48-54.
11. Takedachi M, Murakami S. [Present status of periodontal regeneration - FGF-2 and Teriparatide -]. Clin Calcium. 2012 Jan;22(1):99-104. Japanese. PMID: 22201105.
12. Bashutski JD, Eber RM, Kinney JS, Benavides E, Maitra S, Braun TM, Giannobile WV, McCauley LK. The impact of vitamin D status on periodontal surgery outcomes. J Dent Res. 2011 Aug;90(8):1007-12. doi: 10.1177/0022034511407771. Epub 2011 May 9. PMID: 21555774; PMCID: PMC3170167.
13. Kuchler U, Luvizuto ER, Tangl S, Watzek G, Gruber R. Short-term Teriparatide Delivery and Osseointegration: a Clinical Feasibility Study. *Journal of Dental Research*. 2011;90(8):1001-1006. doi:10.1177/0022034511407920
14. Bashutski JD, Eber RM, Kinney JS, Benavides E, Maitra S, Braun TM, Giannobile WV, McCauley LK. Teriparatide and osseous regeneration in the oral cavity. N Engl J Med. 2010 Dec 16;363(25):2396-405. doi: 10.1056/NEJMoa1005361. Epub 2010 Oct 16. PMID: 20950166; PMCID: PMC5695223.
15. Moore AE, Blake GM, Taylor KA, Rana AE, Wong M, Chen P, Fogelman I. Assessment of regional changes in skeletal metabolism following 3 and 18 months of teriparatide treatment. J Bone Miner Res 2010: 25: 960-7.
16. Miyauchi A et al. Effects of teriparatide on bone mineral density and bone turnover markers in Japanese subjects with osteoporosis at high risk of fracture in a 24-month clinical study: 12-month, randomized, placebo-controlled, double-blind and 12-month open-label phases. Bone. 2010 Sep;47(3):493-502. doi: 10.1016/j.bone.2010.05.022.
17. Lindsay, R., Miller, P., Pohl, G. et al. Relationship between duration of teriparatide therapy and clinical outcomes in postmenopausal women with osteoporosis. Osteoporos Int 20, 943–948 (2009).
18. Recker RR, Marin F, Ish-Shalom S, Möricke R, Hawkins F, et al. Comparative effects of teriparatide and strontium ranelate on bone biopsies and biochemical markers of bone turnover in postmenopausal women with osteoporosis. J Bone Miner Res. 2009;24:1358-68.
19. Hwang JS, Tu ST, Yang TS. Teriparatide vs. calcitonin in the treatment of Asian postmenopausal women with established osteoporosis. Osteoporos Int. 2006;17:373-78.
20. Deal C, Omizo M, Schwartz EN, et al. Combination teriparatide and raloxifene therapy for postmenopausal osteoporosis: results from a 6-

month double-blind placebo-controlled trial. and cancellous bone structure. J Bone Miner Res. 2005;20:1905-11.

21. J. Christopher Gallagher, Harry K. Genant, Gerald G. Crans, Socorro Juan Vargas, John H. Krege, Teriparatide Reduces the Fracture Risk Associated with Increasing Number and Severity of Osteoporotic Fractures, *The Journal of Clinical Endocrinology* & Metabolism, Volume 90, Issue 3, 1 March 2005, Pages 1583–1587, https://doi.org/10.1210/jc.2004-0826.
22. Joel S. Finkelstein, Benjamin Z. Leder, Sherri-Ann M. Burnett, Jason J. Wyland, Hang Lee, Amanda Victoria de la Paz, Kate Gibson, Robert M. Neer, Effects of Teriparatide, Alendronate, or Both on Bone Turnover in Osteoporotic Men, The Journal of Clinical Endocrinology & Metabolism, Volume 91, Issue 8, 1 August 2006, Pages 2882–2887, https://doi.org/10.1210/jc.2006-0190