H.L. Chan¹ and L.K. McCauley^{1,2*}¹Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, Ann Arbor, MI, USA; and²Department of Pathology, University of Michigan, Medical School, Ann Arbor, MI, USA; *corresponding author, mccauley@umich.edu*J Dent Res* 92(1):18-25, 2013**ABSTRACT**

Parathyroid hormone (PTH) is known for its ability to 'build' bone, with research in this area centered on its use as an osteoporosis therapeutic. Recent interest has developed regarding its potential for regenerative applications such as fracture healing and osseous defects of the oral cavity. Many years of investigation using murine gene-targeted models substantiate a role for signaling at the PTH/PTH-related protein (PTHrP) receptor (PPR) in intramembranous bone formation in the craniofacial region as well as in tooth development. Pre-clinical studies clearly support a positive role of intermittent PTH administration in craniofacial bones and in fracture healing and implant integration. A few human clinical studies have shown favorable responses with teriparatide (the biologically active fragment of PTH) administration. Favorable outcomes have emerged with teriparatide administration in patients with osteonecrosis of the jaw (ONJ). New delivery strategies are in development to optimize targeted application of PTH and to help maximize local approaches. The promising host-modulating potential of PTH requires more information to further its effectiveness for craniofacial regeneration and osseous wound-healing, including a better delineation of cellular targets, temporal effects of PTH action, and improved approaches for local/targeted delivery of PTH.

KEY WORDS: anabolic, bone, osseointegration, osteonecrosis, osteoblast, teriparatide.

Parathyroid Hormone Applications in the Craniofacial Skeleton

INTRODUCTION

Teriparatide is a recombinant formulation containing the biologically active first 34 amino acids of human parathyroid hormone (rhPTH) and is approved by the US Food and Drug Administration (FDA) for the treatment of osteoporosis. Recently, interests in its clinical application have emerged for bone regeneration in localized osseous defects and fractures (Skripitz *et al.*, 2000; Barnes *et al.*, 2008; Aspenberg *et al.*, 2010; Bashutski *et al.*, 2010). Animal models with/without induced osteoporosis 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 (Kawane *et al.*, 2002; Rowshan *et al.*, 2010; Valderrama *et al.*, 2010). 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 anti-resorptive drugs (Tsai *et al.*, 2010; Lee *et al.*, 2011; Kwon *et al.*, 2012). This review will update research on the impact of PTH in the craniofacial skeletal, regeneration applications, and future prospects for clinical benefits of PTH therapy.

Positive actions of PTH on vertebral and appendicular bone density have been well-documented; however, whether craniofacial bones respond to PTH similarly is still not clear. Since developmental aspects of craniofacial bone formation are different when compared with those of the other skeletal sites, mechanisms of PTH action may vary based on location. Craniofacial bones are formed by intramembranous ossification, whereas long bones and vertebrae are formed by endochondral ossification. Therefore, experimental results pertaining to the effect of PTH on other skeletal sites should be taken into account when craniofacial applications are considered, and direct translation to craniofacial bone should be approached with caution until more detailed comparative studies are available.

ANIMAL MODELS WITH INDUCED OSTEOPOROSIS

Studies in rats (Miller *et al.*, 1997; Nakajima *et al.*, 2000; Kawane *et al.*, 2002) and rabbits (Bellido *et al.*, 2010) evaluated the effect of PTH on craniofacial bones affected by osteoporosis. Osteoporosis was induced with ovariectomy or in combination with glucocorticoid application or extraction of opposing teeth. Intermittent rhPTH (1-34) or rhPTH (1-84) was administered, and bone quality and quantity were evaluated. These studies suggest that

DOI: 10.1177/0022034512464779

Received July 28, 2012; Last revision September 20, 2012; Accepted September 22, 2012

© International & American Associations for Dental Research

alveolar bone is susceptible to osteoporosis and at the same time more responsive to PTH treatment, as evidenced by greater increases in bone density in the molar region vs. other regions of the jaw. This might be related to a higher bone remodeling rate in the alveolar bone, suggested by animal studies but not yet systematically investigated in humans. Dose- and time-dependent anabolic effects of PTH in the molar region of the mandible were demonstrated, as well as a greater increase in bone mineral density with rhPTH (1-34) vs. rhPTH (1-84) (Kawane *et al.*, 2002). In a ligature-induced periodontitis model, PTH (40 µg/kg), 3 times a wk for 30 days effectively prevented bone loss in periodontal-disease-induced ovariectomized rats (Marques *et al.*, 2005), suggesting that PTH may not only build bone lost to disease but can also prevent inflammatory-mediated bone loss.

ANIMAL MODELS WITHOUT INDUCED OSTEOPOROSIS

Several studies have investigated the effect of PTH on maxillofacial bone healing in animals without osteoporosis (Andreassen and Cacciafesta, 2004; Jung *et al.*, 2007a,b; Valderrama *et al.*, 2010). PTH was applied intermittently in combination with guided bone regeneration in a rat model (Andreassen and Cacciafesta, 2004). Critical-sized bony defects (5-mm diameter) were created in parietal bone and covered by expanded polytetrafluoroethylene membranes. The test group was treated with human PTH (1-34) (60 µg/kg) for 35 days. Dry and ash weight as well as mechanical strength of tissue harvested from the defects were significantly higher with PTH administration. Locally delivered PTH was also used to facilitate bone regeneration (Jung *et al.*, 2007a,b; Valderrama *et al.*, 2010). Polyethylene-glycol matrices carrying PTH were applied to surgically created bony defects surrounding implants. At 12 wks, sites treated with 20 µg/mL PTH (1-34) yielded a significantly higher fraction of new bone compared with sites treated with the carrier alone and without any treatment, while the new bone fraction in PTH-treated sites was comparable with that in sites grafted with autogenous bone. The same agent was tested in combination with hydroxyapatite/tricalcium phosphate granules for bone regeneration in rabbit calvariae (Jung *et al.*, 2007b). Compared with groups with bone graft alone and those that healed spontaneously, the addition of synthetic PTH increased the area of bone formation by 1.6- and 2.3-fold, respectively. Analysis of these data suggests that locally delivered and continuously released PTH could enhance bone healing, although the exact mechanisms are not known. Another recent study also showed positive effects of systemically administered rhPTH (1-34) (15 µg PTH/kg/day) on new bone formation in critical-sized calvarial defects (Yun *et al.*, 2010). Interestingly, when the grafting material β-TCP was utilized, it dampened the PTH increase in bone fill. Thus, PTH might act as a stand-alone or, in certain instances, as an adjunctive agent for enhancing bone healing around implants and teeth in systemically healthy patients.

Investigators established a rat mandible model to examine the effect of rhPTH (1-34) on fracture healing (Rowshan *et al.*, 2010). Radiographic healing was significantly enhanced in the

early phase (7 days) with PTH application (10 µg/kg), evidenced by greater density at the fracture line. By 21 days, there was histologic evidence of greater bone in the PTH group, but no difference in radiographic signs of bone healing between the vehicle and PTH-treatment group. In a mandibular distraction osteogenesis model in the rat, rats receiving rhPTH (1-34) (60 µg/kg) exhibited greater bone volume at the end of the 3-week consolidation phase (Ali *et al.*, 2012). Analysis of these data may suggest a temporal nature to the advantaged bone healing found in association with PTH and may also reflect the nature of the rat model, which has robust osseous healing potential over time regardless of treatment.

CRANIOFACIAL IMPACT OF PTH/PTHrP SIGNALING IN DEVELOPMENT AND DISEASE

Blomstrand Chondrodysplasia (OMIM#215045) is a hereditary condition characterized by advanced skeletal maturation, shortened long bones, and increased bone density. A mutation in exon 3 of PTHR1(PPR) gene is responsible for this fatal condition (Jobert *et al.*, 1998). In humans, the absence of functional PPRs not only affects endochondral bones, but also results in ankylosed and distorted teeth (Wysolmerski *et al.*, 2001), suggesting that PTHrP may be important for maintenance of the periodontal ligament space during development and raising the possibility that PTH could also function at these sites after growth. Along with analysis of pre-clinical data suggesting that PPR signaling functions in maintenance of the periodontal ligament and is essential for tooth eruption (Philbrick *et al.*, 1998; Boabaid *et al.*, 2004), this merits further consideration for patients with primary eruption failure. Since ablation of the PTH gene has not been associated with any overt dental or alveolar bone alterations (Liu *et al.*, 2009), PTHrP is likely the important factor in craniofacial development.

Classically, excess parathyroid hormone, such as found in primary hyperparathyroidism (HPT), has been associated with the loss of alveolar lamina dura, but contemporary findings differ, likely due to differences in the diagnosis of HPT. A more contemporary study (Padbury *et al.*, 2006) evaluating oral health in patients with primary HPT did not find alterations in periodontal findings such as attachment level, alveolar bone, and probing depths, but did find a greater incidence of tori (bony growths in the oral cavity) and reduced cortical bone thickness at the angle of the mandible. It was concluded that PTH showed signs of catabolic and anabolic activity in humans with no adverse effects on the periodontium. Frankenthal *et al.*, studying hemodialysis patients, reported insignificant periodontal findings in humans with secondary hyperparathyroidism (Frankenthal *et al.*, 2002). The subtle findings and low numbers of reports in this area suggest that chronic endogenously produced PTH has minimal impact on oral health.

RECENT INVESTIGATIONAL IMPLICATIONS OF rhPTH (1-34)

Teriparatide has been approved by the FDA for the treatment of the following conditions: (1) women with post-menopausal

Table 1. Human Studies of Teriparatide Administration for Periodontal and Implant Applications

Therapeutic Applications	Ref.	Study Design	N	Location	Intervention	Main Outcome Variables	Results
Periodontal regeneration	Bashutski <i>et al.</i> (2010)	RCT	20/gp	max+ mand	T: sx + 6 wks PTH + suppl C: sx + placebo + suppl	PD, CAL, & linear osseous defect resolution	Greater linear bone gain, PD reduction, & CAL gain at 1 yr
Implant osseointegration	Kuchler <i>et al.</i> (2011)	RCT	12/gp	mand	T: 2 MI + 2 SI + 4 wks PTH C: 2 MI + 2 SI MI	NBV/TV, BV/TV, NBIC & BIC	Trends of favorable outcomes for the PTH group

RCT = randomized clinical trial; max = maxilla; mand = mandible; suppl = supplements (Ca and Vitamin D); T = treatment; C = control; sx = surgery; PD = probing depth; CAL = clinical attachment level; SSD = statistically significantly different; MI = mini-implants; SI = standard implants; BV = bone volume; NBV = new BV; TV = total volume; BIC = bone-to-implant contact; NBIC = new BIC.

Table 2. Human Case Reports of Teriparatide Administration for Treatment of ONJ

Reference	N	Location	Medical Condition	Type of BP	Duration (yrs)	Trigger Event	Stage	Duration of PTH for Clinical Resolution
Cheung and Seeman (2010)	1	Mand	OP	Oral	10	ext	1	8 wks
Harper and Fung (2007)	1	Max	OP	Oral	1	ext	2	3 mos
Kwon <i>et al.</i> (2012)	6	5 mand & 1 max	NA	Oral	3 to 8	NA	2 or 3	1-3 mos
Lau and Adachi (2009)	1	max & mand	OP	Oral & IV	10	ext	2	2 mos
Lee <i>et al.</i> (2011)	1	Mand	OP	Oral	5	ext	2	6 mos
Narongroeknawin <i>et al.</i> (2010)	1	Max	OP	Oral	5	imp	1	4 mos
Narváez <i>et al.</i> (2012)	1	Mand	OP	NS	32	spon	NS	No resolution
Tsai <i>et al.</i> (2010)	1	Mand	NA	Oral	4	imp	3	5 mos

Max = maxilla; mand = mandible; NA = not available; NS = not specified; OP = osteoporosis; BP = bisphosphonate; ext = extraction; imp = implant; spon = spontaneously.

osteoporosis who are at high risk of fracture or who have failed or been intolerant of previous osteoporosis therapy, (2) men with idiopathic or hypogonadal osteoporosis who are at high risk of fracture or who have failed or been intolerant of previous osteoporosis therapy, and (3) men and women with glucocorticoid-induced osteoporosis. Currently published clinical implications are summarized in Tables 1 and 2. One randomized clinical trial (Bashutski *et al.*, 2010) and a case report (Bashutski *et al.*, 2012) investigated the adjunctive benefits of using teriparatide for treating patients with moderate to severe chronic periodontitis. Patients self-administered either daily injections of teriparatide (20 µg) or placebo for 6 wks, in addition to oral calcium and vitamin D and in conjunction with periodontal surgery. At 1 yr, the test group had significantly greater radiographic linear resolution of intrabony defects. Interestingly, patient outcomes in this study were found to be associated with baseline levels of serum 1,25 dihydroxyvitamin D3, with significantly poorer outcomes when patients in either the vehicle or teriparatide group had baseline levels < 20 ng/dL (Bashutski *et al.*, 2011).

Another study evaluated the ability of teriparatide to enhance osseointegration of dental implants (Kuchler *et al.*, 2011). Patients with edentulous lower arches planned for the insertion

of 2 implants to support overdentures had 2 additional mini-implants placed during the surgery. Half of the patients received teriparatide (20 µg) for 4 wks, and the other half had no drug administration. Bone histomorphometry revealed trends toward a positive teriparatide effect on new bone-volume-per-tissue-volume (NBV/TV) and new bone-to-implant-contact (NBIC), but no significant differences were found. Possible reasons might include the small sample size and/or use of smooth mini-implants.

TERIPARATIDE AND OSTEONECROSIS OF THE JAW

Osteonecrosis of the jaw (ONJ) associated with the use of bone anti-resorptive agents is a significant concern. Because of its anabolic actions, teriparatide has been used off-label to treat patients with ONJ, with favorable results (Harper and Fung, 2007; Lau and Adachi, 2009; Cheung and Seeman, 2010; Narongroeknawin *et al.*, 2010; Tsai *et al.*, 2010; Lee *et al.*, 2011; Kwon *et al.*, 2012; Narvaez *et al.*, 2012). One to 6 mos after teriparatide treatment, most cases, with the exception of one (Narvaez *et al.*, 2012), demonstrated clinical resolution of the signs and symptoms of ONJ. The failed response to teriparatide

treatment in the one case was speculated to be associated with the concomitant use of immunosuppressive drugs for controlling rheumatoid arthritis.

PRE-CLINICAL STUDIES PROVIDE INSIGHTS INTO FUTURE POTENTIAL USES FOR PTH

Because of limited supply, high resorption rate, and patient morbidity, autogenous bone has largely been replaced by allografts and biomaterials. Commonly used biomaterials include methyl methacrylate, hydroxyapatite, calcium phosphate, porous polyethylene implants, titanium implants, and others. Long healing times and post-operative complications, *e.g.*, delayed unions or non-unions between host bone and biomaterials, are unsolved issues. With the emergence of tissue-engineering concepts, the application of biological agents has the potential to accelerate or enhance wound-healing processes (Kaigler *et al.*, 2006). PTH shows potential for facilitating regeneration of the craniofacial structures. In particular, the use of PTH might provide benefits to a broad population undergoing the following reconstructive procedures: major craniofacial surgeries, implant-related regeneration, and treatment of ONJ.

Major Craniofacial Surgeries

Critical-sized defects remain a challenge to reconstructive surgeons. Allografts, because of their lack of remodeling and limited osteogenesis, are associated with high rates of clinical failure. Animal studies have been designed to investigate the adjunctive effect of PTH on the healing of devitalized allografts used to repair critical femoral defects (Jacobson *et al.*, 2011; Reynolds *et al.*, 2011). PTH significantly enhanced callus formation and graft-host integration, along with 2-fold increases in normalized callus volume and higher mechanical strength of the graft-host junction at 6 wks (Reynolds *et al.*, 2011). The same group also demonstrated better healing results with PTH and β -TCP as the scaffold in the rat model (Jacobson *et al.*, 2011). These animal studies serve as support for further investigation of the effect of PTH on large defects.

Surgeries to correct jaw relationships typically involve osteotomy of either or both jaws, followed by repositioning the jaws to acquire ideal alignment and fixation. Post-operative discomfort from temporary immobilization of the jaw would be greatly alleviated if solidification between the gaps of bone segments could be expedited. The effect of PTH on the healing of closed fractures in long bones of rodents has been studied (Warden *et al.*, 2009; Komrakova *et al.*, 2010). It is generally reported that the volume, quality, and mechanical strength of the callus are increased when it is treated with systemically administered PTH. For mandibular fractures in rats, PTH enhanced early healing (Rowshan *et al.*, 2010). Clinical trials also showed that PTH accelerated fracture-healing in pelvic (Peichl *et al.*, 2011) and distal radial (Aspenberg and Johansson, 2010) fractures. In light of its positive role on fracture healing in animal and human studies, PTH might benefit patients who undergo orthognathic surgeries by reducing healing time.

Dental Implant and Implant-related Bone Augmentation Procedures

Dental implants are currently the standard of care for replacing missing teeth. Without augmentation procedures, alveolar bone quality and quantity are often inadequate to accommodate implants. Several surgical techniques can be used at various stages of implant therapy to augment bone, *e.g.*, socket/ridge augmentation, guided bone regeneration (GBR), block grafts, and distraction osteogenesis. Animal studies have demonstrated that PTH in combination with GBR and bone grafts could enhance alveolar bone formation (Andreassen and Cacciafesta, 2004; Jung *et al.*, 2007a,b; Valderrama *et al.*, 2010). In fact, alveolar bone, *vs.* other parts of the mandible and maxilla, has been found to be particularly responsive to PTH (Kawane *et al.*, 2002). In the rabbit model, treatment with PTH during distraction osteogenesis resulted in substantially higher mineralized tissue volume, mineral content, and bending strength (Aleksyniene *et al.*, 2009). Significantly increased mechanical strength and bone density were also noted when PTH was applied during the consolidation period in rats, suggesting that only a short-course treatment of PTH is needed (Seebach *et al.*, 2004). PTH might synergize the treatment outcome achieved by current available regenerative procedures for implant therapy.

Although implants can function well in most of the population, a subset of patients has higher failure rates that may be due to their medical conditions. Animal models have shown a positive role of PTH for treating impaired wound healing. Delayed wound healing was induced by daily injection of prednisone, followed by the creation of 1-mm defects in the ulnae of rabbits (Bostrom *et al.*, 2000). All animals treated with a PTHrP analog achieved radiographic union at 6 wks, compared with only 20% in the control group. In addition, PTHrP-treated rabbits had greater radiographic intensity, larger callus areas, and greater stiffness and torque in ulnae. Ovariectomized rats with surgical defects created in tibiae were treated with PTH and showed enhanced fracture healing and increased capillary density in limb muscles (Komrakova *et al.*, 2010).

Results from human studies regarding the use of PTH in medically compromised patients are promising. Post-menopausal women who had sustained a distal radial fracture were randomly assigned to 8 wks of once-daily injections of placebo or 20 or 40 μ g teriparatide (Aspenberg *et al.*, 2010). The time to healing was shorter with low-dose teriparatide than with placebo (7.4 and 9.1 wks, respectively). *Post hoc* subgroup analysis of the qualitative appearance of the callus 5 wks after fracture showed that teriparatide improved early callus formation (Aspenberg and Johansson, 2010). In case reports, delayed unions were successfully treated with teriparatide therapy (Oteo-Alvaro and Moreno, 2010; Rubery and Bukata, 2010). These clinical reports suggest a potential role for PTH therapy in compromised wound-healing.

Interestingly, a case report of teriparatide use in a patient with the osteopetrotic condition pycnodysostosis failed to show an anabolic response to PTH (Chavassieux *et al.*, 2008). Human clinical trials where teriparatide was administered along with bisphosphonates showed a blunted anabolic effect, suggesting that osteoclasts are a requisite for PTH actions in building bone

Figure. Overview of the impact of PTH 1-34 on the craniofacial skeleton. Most studies have been performed in rodent models (left), with positive outcomes particularly in the mandible and calvaria. Positive data are now emerging in humans (right) in the areas of periodontal disease, implant integration, and resolution of osteonecrosis of the jaw (ONJ).

(Black *et al.*, 2003). Since compromises in osteoclast function can arise at various stages of differentiation (Wang and McCauley, 2011), it will be interesting to see how PTH pairs with other anti-resorptive strategies. In animal models, anabolic actions of PTH were totally absent in the osteopetrotic *c-fos* knock-out mice lacking osteoclasts, whereas PTH retained its anabolic actions in the osteopetrotic *c-src* knock-out mice, which have osteoclasts present but with compromised function (Koh *et al.*, 2005). Indeed, it is not likely as simple as being an osteoclast-dependent process, since analysis of more recent human clinical data showed additive effects of zoledronic acid and teriparatide on hip and spine BMD values (Cosman *et al.*, 2011).

Treatment for Osteonecrosis of the Jaw (ONJ)

Due to misunderstood risk/benefit ratios, patients who take bisphosphonates might be deprived of the benefits of certain dental procedures thought to be associated with the development of ONJ. The pathogenesis of bisphosphonate-related osteonecrosis of the jaw has been speculated to be due to the impact of bisphosphonates on osteoclast survival, epithelial cells, endothelial cells, and immune cells (Yamashita *et al.*, 2010). Bisphosphonates exert their anti-resorptive activity by suppression of osteoclasts. A few clinical cases have reported the successful off-label use of teriparatide for treating ONJ (Harper and Fung, 2007; Lau and Adachi, 2009; Cheung and Seeman, 2010; Narongroeknawin *et al.*, 2010; Tsai *et al.*, 2010; Lee *et al.*, 2011; Kwon *et al.*, 2012; Narvaez *et al.*, 2012). Teriparatide increases bone remodeling and has been reported to reduce microdamage accumulation in the bone, a possible etiology of ONJ. As a result, teriparatide might assist in removing

necrotic bone and accelerating healing in ONJ patients. Large-scale studies and/or well-characterized animal models are necessary to evaluate the efficacy of teriparatide for treating or even preventing the occurrence of ONJ, although this is difficult due to the low incidence of ONJ with oral administration of bisphosphonates for treatment of non-malignant bone diseases. It might be more advantageous to consider whether teriparatide can treat ONJ in patients receiving IV bisphosphonates for cancers, since the incidence is much higher than for metabolic bone disease patients. However, such trials would have to be designed with care, because, currently, teriparatide is contraindicated for patients with metastatic cancer.

OUTSTANDING QUESTIONS AND FUTURE DIRECTIONS

Concerns on the Development of Osteosarcoma

The use of PTH 1-34 to improve bone quantity and quality has been substantiated in numerous animal and human studies (Fig.). Still, concerns exist. Teriparatide has a “black box” warning because of the occurrence of osteosarcomas in rats administered high doses of teriparatide (from 3- to 58-fold the human equivalent dose) starting at 2 wks of age and continued for their lifetimes (approximately 75 human yr equivalents) (Vahle *et al.*, 2002). A follow-up study did not show malignant bone tumors with doses 3-fold or lower than the human equivalent dose (Vahle *et al.*, 2004). Monkeys receiving teriparatide did not show bone-proliferative lesions over a 4.5-year interval of observation after 18 mos of treatment (Vahle *et al.*, 2008). Apparently, the dose and duration of the treatment and species differences are the important variables in teriparatide-associated

bone tumors. Therefore, it is important that we learn how to optimize the therapeutic window during which teriparatide can be used. Nonetheless, because teriparatide resulted in an increased incidence of osteosarcomas in rats, it is contraindicated in patients at increased risk of osteosarcoma (those with Paget's disease of bone, open epiphyses, a history of irradiation involving the skeleton, or an unexplained elevation of skeletal alkaline phosphatase). The incidence of osteosarcomas in women 50 yrs old or older is approximately 1 in 250,000. The actual incidence of osteosarcoma in users of teriparatide is not known; rare cases have been reported, consistent with the background incidence (Harper *et al.*, 2007). Teriparatide should also not be administered to patients with primary or any form of secondary untreated or unresolved hyperparathyroidism.

Critical Treatment Time

Since the primary goal of using PTH for craniofacial defects is to enhance healing, the timing of applying PTH in relation to the stages of bone healing becomes critical. Whether the therapeutic anabolic window of teriparatide for metabolic diseases (Canalis *et al.*, 2007) can be applied to the healing of bone-reparative procedures is not known. For elective surgeries, *e.g.*, ridge augmentation and implant therapy, when should PTH be administered to maximize its anabolic effect? It is arguable that PTH should be given prior to the surgery, so that bone remodeling can be activated ahead of bone healing, which is the case in the study of periodontal patients in whom teriparatide was initiated 3 days prior to a surgical procedure (Bashutski *et al.*, 2010). For treatment of delayed or non-healed wounds, *e.g.*, ONJ, no information is available with regard to the temporal administration of PTH therapy to achieve optimal results. The optimal duration of the PTH treatment for bone regeneration is another unsolved question. It is reasonable to assume that PTH treatment should not extend beyond 6 mos, which is the normal time range for bone healing. However, how short should the treatment be to minimize possible adverse outcomes, patient discomfort, and optimize patient compliance? In some clinical studies (Aspenberg *et al.*, 2010; Bashutski *et al.*, 2010; Kuchler *et al.*, 2011), the duration ranged from 4 to 8 wks. Again, further studies are warranted to optimize the timing and duration of PTH therapy for bone-regeneration procedures.

Drug Delivery System

Currently, teriparatide is administered systemically, which has drawbacks—including the requirement for self-injection and the 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 circumventing possible adverse side-effects resulting from systematic administration, decreasing dose or number of dosages, and maintaining local agent levels within a desirable range. Poly (lactic-co-glycolic acid) (PLGA) microspheres were formulated to carry and control the release of PTH (Wei *et al.*, 2004). Subsequently, a biodegradable polymer, poly (l-lactic acid) (PLLA)-based implantable delivery system containing alternative layers of polyanhydride isolation layers and PTH-loaded alginate layers

was developed (Liu *et al.*, 2007). This approach demonstrated released PTH to be biologically active and holds promise for both systemic and local therapies. Clinical studies will be required to validate the results of these *in vitro* studies.

In summary, the intersection of expanding pre-clinical regenerative studies, gene-targeted models, and new mechanistic insights with emerging clinical studies supports the merit of PTH for improving craniofacial-regenerative strategies. Clarification of important aspects that could further improve the effectiveness of PTH use include a better delineation of the cellular targets (direct and indirect) for PTH action, the temporal effects of PTH action during regeneration, as well as the best approach for local/targeted delivery of PTH for dental applications.

ACKNOWLEDGMENTS

The authors do not have any current financial interests in the products or information listed in the paper. LKM previously received pilot funding from Eli Lilly for a clinical study using teriparatide in patients with periodontal disease. This study was supported by the US National Institutes of Health (grants DK53904 and DE022327). The authors declare no other potential conflicts of interest with respect to the authorship and/or publication of this article.

REFERENCES

- Aleksyniemi R, Thomsen JS, Eckardt H, Bundgaard KG, Lind M, Hvid I (2009). Parathyroid hormone PTH(1-34) increases the volume, mineral content, and mechanical properties of regenerated mineralizing tissue after distraction osteogenesis in rabbits. *Acta Orthop* 80:716-723.
- Ali MN, Kobayashi T, Tanaka M, Ohshima H, Ejiri S, Saito C (2012). Effects of intermittent parathyroid hormone treatment on new bone formation during distraction osteogenesis in the rat mandible. *Oral Surg Oral Med Oral Pathol Oral Radiol* 114:e36-e42.
- Andreassen TT, Cacciafesta V (2004). Intermittent parathyroid hormone treatment enhances guided bone regeneration in rat calvarial bone defects. *J Craniofac Surg* 15:424-427.
- Aspenberg P, Johansson T (2010). Teriparatide improves early callus formation in distal radial fractures. *Acta Orthop* 81:234-236.
- Aspenberg P, Genant HK, Johansson T, Nino AJ, See K, Krohn K, *et al.* (2010). Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. *J Bone Miner Res* 25:404-414.
- Barnes GL, Kakar S, Vora S, Morgan EF, Gerstenfeld LC, Einhorn TA (2008). Stimulation of fracture-healing with systemic intermittent parathyroid hormone treatment. *J Bone Joint Surg Am* 90(Suppl 1):120-127.
- Bashutski JD, Eber RM, Kinney JS, Benavides E, Maitra S, Braun TM, *et al.* (2010). Teriparatide and osseous regeneration in the oral cavity. *N Engl J Med* 363:2396-2405.
- Bashutski JD, Eber RM, Kinney JS, Benavides E, Maitra S, Braun TM, *et al.* (2011). The impact of vitamin D status on periodontal surgery outcomes. *J Dent Res* 90:1007-1012.
- Bashutski JD, Kinney JS, Benavides E, Maitra S, Braun TM, Giannobile WV, *et al.* (2012). Systemic teriparatide administration promotes osseous regeneration of an intrabony defect: a case report. *Clin Adv Periodontics* 2:66-71.
- Bellido M, Lugo L, Castaneda S, Roman-Blas JA, Rufian-Henares JA, Navarro-Alarcon M, *et al.* (2010). PTH increases jaw mineral density in a rabbit model of osteoporosis. *J Dent Res* 89:360-365.
- Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, *et al.* (2003). The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med* 349:1207-1215.

- Boabaid F, Berry JE, Koh AJ, Somerman MJ, McCauley LK (2004). The role of parathyroid hormone-related protein in the regulation of osteoclastogenesis by cementoblasts. *J Periodontol* 75:1247-1254.
- Bostrom MP, Gamradt SC, Asnis P, Vickery BH, Hill E, Avnur Z, et al. (2000). Parathyroid hormone-related protein analog RS-66271 is an effective therapy for impaired bone healing in rabbits on corticosteroid therapy. *Bone* 26:437-442.
- Canalis E, Giustina A, Bilezikian JP (2007). Mechanisms of anabolic therapies for osteoporosis. *N Engl J Med* 357:905-916.
- Chavassieux P, Asser Karsdal M, Segovia-Silvestre T, Neutsky-Wulff AV, Chapurlat R, Boivin G, et al. (2008). Mechanisms of the anabolic effects of teriparatide on bone: insight from the treatment of a patient with pycnodyostosis. *J Bone Miner Res* 23:1076-1083.
- Cheung A, Seeman E (2010). Teriparatide therapy for alendronate-associated osteonecrosis of the jaw. *N Engl J Med* 363:2473-2474.
- Cosman F, Eriksen EF, Recknor C, Miller PD, Guanabens N, Kasperk C, et al. (2011). Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. *J Bone Miner Res* 26:503-511.
- Frankenthal S, Nakhoul F, Machtei EE, Green J, Ardekian L, Laufer D, et al. (2002). The effect of secondary hyperparathyroidism and hemodialysis therapy on alveolar bone and periodontium. *J Clin Periodontol* 29:479-483.
- Harper KD, Kregge JH, Marcus R, Mitlak BH (2007). Osteosarcoma and teriparatide? *J Bone Miner Res* 22:334.
- Harper RP, Fung E (2007). Resolution of bisphosphonate-associated osteonecrosis of the mandible: possible application for intermittent low-dose parathyroid hormone [rhPTH(1-34)]. *J Oral Maxillofac Surg* 65:573-580; erratum in *J Oral Maxillofac Surg* 65:1059, 2007.
- Jacobson JA, Yanoso-Scholl L, Reynolds DG, Dadali T, Bradica G, Bukata S, et al. (2011). Teriparatide therapy and beta-tricalcium phosphate enhance scaffold reconstruction of mouse femoral defects. *Tissue Eng Part A* 17:389-398.
- Jobert AS, Zhang P, Couvineau A, Bonaventure J, Roume J, Le Merrer M, et al. (1998). Absence of functional receptors for parathyroid hormone and parathyroid hormone-related peptide in Blomstrand chondrodysplasia. *J Clin Invest* 102:34-40.
- Jung RE, Cochran DL, Domken O, Seibl R, Jones AA, Buser D, et al. (2007a). The effect of matrix bound parathyroid hormone on bone regeneration. *Clin Oral Implants Res* 18:319-325.
- Jung RE, Hämmerle CH, Kokovic V, Weber FE (2007b). Bone regeneration using a synthetic matrix containing a parathyroid hormone peptide combined with a grafting material. *Int J Oral Maxillofac Implants* 22:258-266.
- Kaigler D, Cirelli JA, Giannobile WV (2006). Growth factor delivery for oral and periodontal tissue engineering. *Expert Opin Drug Deliv* 3:647-662.
- Kawane T, Takahashi S, Saitoh H, Okamoto H, Kubodera N, Horiuchi N (2002). Anabolic effects of recombinant human parathyroid hormone (1-84) and synthetic human parathyroid hormone (1-34) on the mandibles of osteopenic ovariectomized rats with maxillary molar extraction. *Horm Metab Res* 34:293-302.
- Koh AJ, Demiralp B, Neiva KG, Hooten J, Nohutcu RM, Shim H, et al. (2005). Cells of the osteoclast lineage as mediators of the anabolic actions of parathyroid hormone in bone. *Endocrinology* 146:4584-4596.
- Komrakova M, Stuermer EK, Werner C, Wicke M, Kolios L, Sehmisch S, et al. (2010). Effect of human parathyroid hormone hPTH (1-34) applied at different regimes on fracture healing and muscle in ovariectomized and healthy rats. *Bone* 47:480-492.
- Kuchler U, Luvizuto ER, Tangl G, Watzek G, Gruber R (2011). Short-term teriparatide delivery and osseointegration: a clinical feasibility study. *J Dent Res* 90:1001-1006.
- Kwon YD, Lee DW, Choi BJ, Lee JW, Kim DY (2012). Short-term teriparatide therapy as an adjunctive modality for bisphosphonate-related osteonecrosis of the jaws. *Osteoporos Int* [Epub ahead of print Jan 5, 2012] (in press).
- Lau AN, Adachi JD (2009). Resolution of osteonecrosis of the jaw after teriparatide [recombinant human PTH-(1-34)] therapy. *J Rheumatol* 36:1835-1837.
- Lee JJ, Cheng SJ, Jeng JH, Chiang CP, Lau HP, Kok SH (2011). Successful treatment of advanced bisphosphonate-related osteonecrosis of the mandible with adjunctive teriparatide therapy. *Head Neck* 33:1366-1371.
- Liu H, Guo J, Wang L, Chen N, Karaplis A, Goltzman D, et al. (2009). Distinctive anabolic roles of 1,25-dihydroxyvitamin D(3) and parathyroid hormone in teeth and mandible versus long bones. *J Endocrinol* 203:203-213.
- Liu X, Pettway GJ, McCauley LK, Ma PX (2007). Pulsatile release of parathyroid hormone from an implantable delivery system. *Biomaterials* 28:4124-4131.
- Marques MR, da Silva MA, Manzi FR, Cesar-Neto JB, Nociti FH Jr, Barros SP (2005). Effect of intermittent PTH administration in the periodontitis-associated bone loss in ovariectomized rats. *Arch Oral Biol* 50:421-429.
- Miller SC, Hunziker J, Mecham M, Wronski TJ (1997). Intermittent parathyroid hormone administration stimulates bone formation in the mandibles of aged ovariectomized rats. *J Dent Res* 76:1471-1476.
- Nakajima M, Ejiri S, Tanaka M, Toyooka E, Kohno S, Ozawa H (2000). Effect of intermittent administration of human parathyroid hormone (1-34) on the mandibular condyle of ovariectomized rats. *J Bone Miner Metab* 18:9-17.
- Narongroeknawin P, Danila MI, Humphreys LG Jr, Barasch A, Curtis JR (2010). Bisphosphonate-associated osteonecrosis of the jaw, with healing after teriparatide: a review of the literature and a case report. *Spec Care Dentist* 30:77-82.
- Narvaez J, Narvaez JA, Gomez-Vaquero C, Nolla JM (2012). Lack of response to teriparatide therapy for bisphosphonate-associated osteonecrosis of the jaw. *Osteoporos Int* [Epub ahead of print Mar 8, 2012] (in press).
- Oteo-Alvaro A, Moreno E (2010). Atrophic humeral shaft nonunion treated with teriparatide (rh PTH 1-34): a case report. *J Shoulder Elbow Surg* 19:e22-e28.
- Padbury AD Jr, Tozum TF, Taba M Jr, Ealba EL, West BT, Burney RE, et al. (2006). The impact of primary hyperparathyroidism on the oral cavity. *J Clin Endocrinol Metab* 91:3439-3445.
- Peichl P, Holzer LA, Maier R, Holzer G (2011). Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. *J Bone Joint Surg Am* 93:1583-1587.
- Philbrick WM, Dreyer BE, Nakhbandi IA, Karaplis AC (1998). Parathyroid hormone-related protein is required for tooth eruption. *Proc Natl Acad Sci USA* 95:11846-11851.
- Reynolds DG, Takahata M, Lerner AL, O'Keefe RJ, Schwarz EM, Awad HA (2011). Teriparatide therapy enhances devitalized femoral allograft osseointegration and biomechanics in a murine model. *Bone* 48:562-570.
- Rowshan HH, Parham MA, Baur DA, McEntee RD, Cauley E, Carriere DT, et al. (2010). Effect of intermittent systemic administration of recombinant parathyroid hormone (1-34) on mandibular fracture healing in rats. *J Oral Maxillofac Surg* 68:260-267.
- Rubery PT, Bukata SV (2010). Teriparatide may accelerate healing in delayed unions of type III odontoid fractures: a report of 3 cases. *J Spinal Disord Tech* 23:151-155.
- Seebach C, Skripitz R, Andreassen TT, Aspenberg P (2004). Intermittent parathyroid hormone (1-34) enhances mechanical strength and density of new bone after distraction osteogenesis in rats. *J Orthop Res* 22:472-478.
- Skripitz R, Andreassen TT, Aspenberg P (2000). Strong effect of PTH (1-34) on regenerating bone: a time sequence study in rats. *Acta Orthop Scand* 71:619-624.
- Tsai KY, Huang CS, Huang GM, Yu CT (2010). More on the resolution of bisphosphonate-associated osteonecrosis of the jaw. *J Rheumatol* 37:675.
- Vahle JL, Sato M, Long GG, Young JK, Francis PC, Engelhardt JA, et al. (2002). Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1-34) for 2 years and relevance to human safety. *Toxicol Pathol* 30:312-321.
- Vahle JL, Long GG, Sandusky G, Westmore M, Ma YL, Sato M (2004). Bone neoplasms in F344 rats given teriparatide [rhPTH(1-34)] are dependent on duration of treatment and dose. *Toxicol Pathol* 32:426-438.

- Vahle JL, Zuehlke U, Schmidt A, Westmore M, Chen P, Sato M (2008). Lack of bone neoplasms and persistence of bone efficacy in cynomolgus macaques after long-term treatment with teriparatide [rhPTH(1-34)]. *J Bone Miner Res* 23:2033-2039.
- Valderrama P, Jung RE, Thoma DS, Jones AA, Cochran DL (2010). Evaluation of parathyroid hormone bound to a synthetic matrix for guided bone regeneration around dental implants: a histomorphometric study in dogs. *J Periodontol* 81:737-747.
- Wang Z, McCauley LK (2011). Osteoclasts and odontoclasts: signaling pathways to development and disease. *Oral Dis* 17:129-142.
- Warden SJ, Komatsu DE, Rydberg J, Bond JL, Hassett SM (2009). Recombinant human parathyroid hormone (PTH 1-34) and low-intensity pulsed ultrasound have contrasting additive effects during fracture healing. *Bone* 44:485-494.
- Wei G, Pettway GJ, McCauley LK, Ma PX (2004). The release profiles and bioactivity of parathyroid hormone from poly(lactic-co-glycolic acid) microspheres. *Biomaterials* 25:345-352.
- Wysolmerski JJ, Cormier S, Philbrick WM, Dann P, Zhang JP, Roume J, et al. (2001). Absence of functional type 1 parathyroid hormone (PTH)/PTH-related protein receptors in humans is associated with abnormal breast development and tooth impaction. *J Clin Endocrinol Metab* 86:1788-1794.
- Yamashita J, McCauley LK, Van Poznak C (2010). Updates on osteonecrosis of the jaw. *Curr Opin Support Palliat Care* 4:200-206.
- Yun JI, Wikesjö UM, Borke JL, Bisch FC, Lewis JE, Herold RW, et al. (2010). 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. *J Clin Periodontol* 37:419-426.