J Clin Periodontol 2010; 37: 739–746 doi: 10.1111/j.1600-051X.2010.01576.x

Journal of Clinical Periodontology

Growth/differentiation factor-5 significantly enhances periodontal wound healing/ regeneration compared with platelet-derived growth factor-BB in dogs

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Kwon H-R, Wikesjö UME, Park J-C, Kim Y-T, Bastone P, Pippig SD, Kim C-K. Growth/differentiation factor-5 significantly enhances periodontal wound healing/ regeneration compared with platelet-derived growth factor-BB in dogs. J Clin Periodontol 2010; 37: 739–746. doi: 10.1111/j.1600-051X.2010.01576.x.

Abstract

Objective: Recombinant human growth/differentiation factor-5 (rhGDF-5) in a particulate β-tricalcium phosphate (β-TCP) carrier is being evaluated to support periodontal regeneration. The objective of this study was to evaluate periodontal wound healing/regeneration following an established clinical (benchmark) protocol including surgical implantation of rhGDF-5/β-TCP in comparison with that following implantation of recombinant human platelet-derived growth factor-BB (rhPDGF) combined with a particulate β-TCP biomaterial using an established canine defect model.

Materials and Methods: Bilateral, 4 × 5 mm (width × depth), one-wall, critical-size, intrabony periodontal defects were surgically created at the mandibular second and fourth pre-molar teeth in five adult Beagle dogs. Defect sites were randomized to receive rhGDF-5/β-TCP or the rhPDGF construct followed by wound closure for primary intention healing. The animals were sacrificed following an 8-week healing interval for histological and histometric examination.

Results: Clinical healing was generally uneventful. Sites receiving rhGDF-5/β-TCP exhibited a significantly enhanced cementum formation compared with sites receiving the rhPDGF construct, averaging ($\pm$ SD) 4.49 ± 0.48 *versus* 2.72 ± 0.91 mm ($p < 0.001$). Similarly, bone regeneration height and area were significantly enhanced at sites receiving rhGDF-5/β-TCP *versus* that of the rhPDGF construct averaging, 3.08 ± 0.74 *versus* 1.29 ± 0.78 mm ($p < 0.001$) and 6.03 ± 1.28 *versus* 2.98 ± 2.61 mm^2 ($p < 0.01$), respectively. Cementum regeneration included cellular/ acellular mixed (extrinsic/intrinsic) fibre cementum at sites receiving rhGDF-5/β-TCP; sites receiving the rhPDGF/β-TCP showed a pre-dominantly acellular cementum. Newly formed cementum generally extended above the adjoining alveolar bone. Both protocols displayed β-TCP residues apparently undergoing resorption. Application of both materials appears safe, as they were associated with limited, if any, adverse events.

Conclusion: rhGDF-5/β-TCP shows a significant potential to support/accelerate periodontal wound healing/regeneration. Application of rhGDF-5/β-TCP appears safe and should be further evaluated in human clinical trials.

Key words: dog; β-TCP; periodontal regeneration; rhGDF-5; rhPDGF; tissue engineering

Accepted for publication 3 March 2010

Conflict of interest and source of funding statement

The research reported herein was conducted at Scil Technology GmbH, Martinsried, Germany, and at Yonsei University College of Dentistry, Seoul, Korea. Drs. Susanne D. Pippig and Patrizia Bastone are employees of Scil Technology. Professor Chong-Kwan Kim received grants from Scil Technology to conduct the studies. Professor Ulf M. E. Wikesjö serves as a consultant to Scil Technology.

Complete regeneration of the periodontal attachment is a highly desirable outcome of periodontal therapy directed at undoing the harms of disease or trauma to the periodontal structures. Experimental studies based on the triad for periodontal regeneration of wound stability, space provision, and conditions for primary intention healing have unraveled a strong innate potential for periodontal regeneration (Polimeni et al. 2006, 2009). Nevertheless, it appears difficult to clinically benefit from this powerful native resource. This perhaps emerges from an incomplete understanding of periodontal wound healing/regeneration, but also and probably more common, challenges met in the clinic with difficulty allow biologic requirements mandated for successful outcomes.

Several additions to gingival flap surgery have been developed, introduced, and are daily evaluated in clinical practice. Such therapeutic additions include non-resorbable and resorbable barrier devices, various bone biomaterials, and more recently products combining scaffolds with matrix, growth, and differentiation factors. Examples of commercially available products include recombinant human bone morphogenetic protein-2 (rhBMP-2) in an absorbable collagen sponge carrier (Choi et al. 2002, Wikesjö et al. 2003d, e), recombinant human platelet-derived growth factor (rhPDGF) combined with a β-tricalcium phosphate (β-TCP) biomaterial (Nevins et al. 2005), and an enamel matrix protein derivative in a propylene glycol alginate vehicle (Heden & Wennström, 2006, Sculean et al. 2008).

Growth/differentiation factor-5 (GDF-5), also known as cartilage-derived morphogenetic protein-1 (Hötten et al. 1994, 1996) is considered for periodontal regenerative procedures (for review see Moore et al. 2010). Briefly, GDF-5 has been shown to enhance the proliferation of human periodontal ligament cells in a dose-dependent order in vitro (Nakamura et al. 2003). GDF-5, -6, and -7 mRNA are expressed in bovine teeth and periodontal tissue development. The dental follicle and odontoblast layer express GDF-5 and -6 mRNA, while GDF-7 mRNA expression is detected in the dental follicle suggesting that GDF-5, -6, and -7 may be potent regulatory molecules in the development of the periodontal attachment (Morotome et al. 1998). Moreover, utilizing in situ hybridization, GDF-5, -6, and -7 mRNA expression have been shown in cells associated with fibre bundle formation and during root formation in developing periodontal tissues in rats (Sena et al. 2003). GDF-5 has also been shown to accelerate tendon/ligament formation and repair in rats (Wolfman et al. 1997, Forslund et al. 2003, Bolt et al. 2007, Dines et al. 2007). Still, other studies have shown that implantation of rhGDF-5 in a β-TCP carrier may accelerate local bone formation following sinus and alveolar augmentation procedures using canine- and porcine-based models (Gruber et al. 2008, Schwarz et al. 2008, Weng et al. 2009). In addition, recent studies have evaluated not only an rhGDF-5/β-TCP candidate treatment for periodontal regeneration but also rhGDF-5 in an absorbable collagen sponge carrier using a critical-size, one-wall, intrabony defect model in dogs (Kim et al. 2009, Lee et al. 2010). Defects sites receiving rhGDF-5/β-TCP responded with an enhanced regeneration of the periodontal attachment compared with rhGDF-5/ACS, indicating that the β-TCP biomaterial is the more effective carrier technology. The objective of this study was to compare the candidate rhGDF-5/β-TCP treatment with an established benchmark, rhPDGF/β-TCP (Nevins et al. 2005), already available to clinical practice.

Materials and Methods

Animals

Five male Beagle dogs, approximately 15 months old, weight 9–13 kg, bred exclusively for biomedical research purposes, were used. The animals exhibited an intact dentition with a healthy periodontium. Animal selection and management, surgical protocol, and preparation followed routines approved by the Institutional Animal Care and Use Committee, Yonsei Medical Center, Seoul, Korea. The animals had an ad libitum access to water and a pelleted laboratory diet with the exception of 8 weeks immediately post-surgery when they were fed a canned soft-dog-food diet (Prescription Diet Canine i/d, Hill's Pet Nutrition Inc., Topeka, KS, USA).

Biomaterials

The rhGDF-5/β-TCP technology (Scil Technology GmbH, Martinsried, Germany) comprises rhGDF-5 coated onto a synthetic β-TCP (Calciresorb, Ceraver Osteal, Roissy, France) at a concentration of 500 μg/g β-TCP using a proprietary protocol. The β-TCP biomaterial includes micro- and macro-porous, irregular, 0.5–1.0-mm-diameter granules of a phase purity $>95\%$ with an average pore diameter of 2 μm, and a pore area of 0.7 m^2/g. The macro-pore diameter ranges between 100 and 400 μm and the pore area is estimated as 1.2 m^2/g (Pöhling et al. 2006). All materials were stored at -80°C until use.

The two-component rhPDGF/β-TCP construct (GEM21s, BioMimetic Therapeutics Inc., Franklin, TN, USA) comprises 0.5 ml rhPDGF-BB (0.3 mg/ml) and 0.5 cm^3 β-TCP. The synthetic β-TCP carrier includes micro- and macro-porous, irregular, 0.3–1.0-mm-diameter granules with a pore diameter ranging from 1 to 500 μm. The rhPDGF/β-TCP construct was applied as directed by the package insert.

Surgical procedures

The surgical protocol and post-surgery procedures followed established routines (Kim et al. 2004, 2005). Briefly, with minor modifications, food was withheld the night preceding surgery. The surgical procedures were performed under general anaesthesia induced by a subcutaneous injection of atropin (0.05 mg/kg; Kwangmyung Pharmaceutical Ind. Co. Ltd., Seoul, Korea) and an intra-venous injection of a combination of xylazine (Rompun, Bayer Korea Co., Seoul, Korea) and Zoletil (Virbac SA, Carros, France) followed by inhalation anaesthesia (Gerolan, Choongwae Pharmaceutical Co., Seoul, Korea). Routine dental infiltration anaesthesia was used at the surgical sites.

The mandibular third pre-molars were surgically extracted before the experimental surgery and the extraction

sites were allowed to heal for 8 weeks. The remaining dentition received oral prophylaxis in conjunction with the extractions.

Experimental surgeries were performed under general anaesthesia by an experienced surgeon (C. K. K.). Buccal and lingual mucoperiosteal flaps were elevated to create critical-size, ''box-type'', 4 × 5 mm (width × height), one-wall intrabony defects at the distal aspect of the second and the mesial aspect of the fourth mandibular pre-molar teeth in right and left jaw quadrants (Fig. 1). Instrumentation with curettes was used to remove the root cementum and to establish a distinct landmark at the base of the defect. Defects were randomized and allocated according to a split-mouth design to either receive rhGDF-5/β-TCP or rhPDGF/β-TCP. The defect sites were filled to the level of the alveolar crest. The mucogingival flaps were advanced, adapted, and sutured using an expanded polytetrafluoroethylene suture material (Gore Tex® Suture CV-5, W. L. Gore & Associates Inc., Flagstaff, AZ, USA).

Post-operative management

The animals received a broad-spectrum antibiotic daily (Cefazoline sodium 20 mg/kg, i.m., 3 days; Yuhan Co.) and a daily topical application of a 0.2% chlorhexidine solution (Hexamedin®, Bukwang Pharmaceutical Co., Seoul, Korea) for infection control. Observations of experimental sites with regard to gingival health, maintenance of suture line closure, oedema, and evidence of tissue necrosis or infection were made daily until suture removal, and at least twice weekly thereafter. The animals were euthanized at 8 weeks post-surgery using an overdose of pentobarbital sodium (90–120 mg/kg, i.v.). Block sections including defect sites and surrounding alveolar bone and mucosal tissues were then collected. Photographic and radiographic recordings were completed intra-surgery, immediately post-surgery, and at 8 weeks post-surgery.

Histological processing

The block specimens were rinsed in sterile saline and immersed in 10% neutral buffered formalin at a volume 10 times that of the tissue block for 10 days. After rinsing in sterile water, the sections were decalcified in 5% formic acid for 14 days, trimmed, dehydrated in a graded ethanol series, and embedded in paraffin. Step-serial sections, 5 μm thick, were cut in a mesial–distal vertical plane, at approximately 80 μm intervals. The sections were stained using haematoxylin/eosin. The four most central sections of each defect site selected based on the width of the root canal were used for the histological and histometric analysis.

Histological analysis

One experienced masked examiner performed the histopathologic evaluation using incandescent and polarized light microscopy (Olympus Multi-view microscope BH2, Tokyo, Japan) including observations of bone regeneration (lamellar and woven bone), residual biomaterial and associated tissue reaction(s), cementum regeneration (cellular/acellular cementum; cementoid/cementum-like layer; intrinsic/extrinsic/mixed fibre cementum), PDL orientation/density (0: no PDL fibres; 1: low-density PDL fibres; 2: moderate-density PDL fibres; 3: high-density PDL fibres, or same as the native adjoining PDL), ankylosis, and undermining root resorption

Histometric analysis

One calibrated masked examiner (Y. T. K.) performed the histometric analysis using a PC-based image analysis system (Image-Pro Plus™, Media Cybernetic, Silver Spring, MD, USA) and incandescent and polarized light microscopy (Olympus Multi-view microscope BH2). The following parameters were analysed for the four central sections (Fig. 2):

- *Defect height*: distance from the apical extension of the root planing to the cemento-enamel junction (CEJ).
- *Epithelial attachment*: distance from the CEJ to the apical extension of an epithelial attachment on the root surface. This parameter included any gingival recession.
- *Cementum regeneration*: distance from the apical extension of the root planing to the coronal extension of the newly formed cementum or a cementum-like substance on the root surface.
- *Connective tissue attachment*: the extent of a non-specific connective tissue attachment was calculated as the defect height minus the sum of cementum regeneration and the epithelial attachment.
- *Bone regeneration (height)*: distance from the apical extension of the root planing to the coronal extension of the newly formed bone along the root surface.

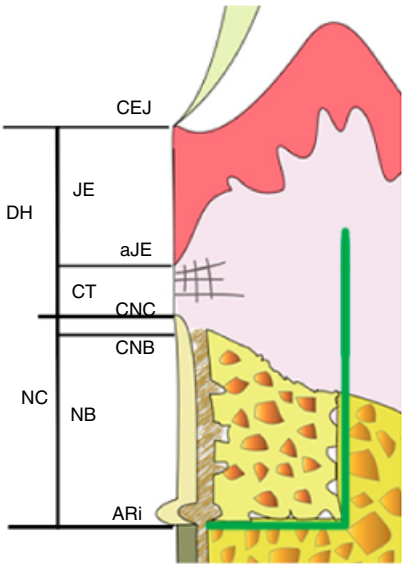

Fig. 2. Landmarks/parameters used in the histometric analysis. The green template serves as a proxy for the defect site for the estimation of bone regeneration area. CEJ, cementoenamel junction; JE, junctional epithelium; aJE, apical extension of junctional epithelium; CT, connective tissue; CNC, coronal extension of new cementum; CNB, coronal extension of newly formed bone; NB, height of newly formed bone; ARi, apical extension of root instrumentation; DH, defect height; NC, height of new cementum.

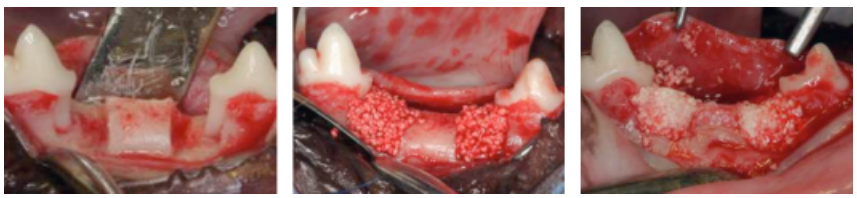

Fig. 1. Critical-size, one-wall, intrabony defects at the distal aspect of the second and the mesial aspect of the fourth mandibular pre-molar teeth (left), and following placement of rhGDF-5/β-TCP (centre) and rhPDGF/β-TCP (right).

- *Bone regeneration (area)*: newly formed bone within a template that served as a standardized proxy for the defect site (shown as an area within the green template in Fig. 2). The template was aligned parallel to the root surface interfacing the apical extension of the root planing.
- *Root resorption*: combined linear heights of distinct resorption lacunae on the planed root.
- *Ankylosis*: combined linear heights of ankylotic union between the regenerated alveolar bone and the planed root.

Statistical analysis

Summary statistics (mean ± SD) based on animal means for the experimental treatments were calculated using the four central sections from each defect, defects being averaged for each experimental group. The statistical comparison between the treatments rhGDF-5/β-TCP and rhPDGF/β-TCP was performed for the paired comparisons in the split-mouth design for the fixed factor treatment and the hierarchical random factors: animal, side (right, left) position (1, 2 and 3, 4; respectively), and replication (1, 2, 3, 4) as an incomplete block design using a mixed linear model. Two-sided p-values are reported for the treatment differences for each individual endpoint without multiplicity adjustment.

Results

Clinical and radiographic observations

All sites including both the rhGDF-5/β-TCP and rhPDGF/β-TCP groups healed uneventfully. Both groups showed radiographic bone formation at the defect sites.

Histologic analysis

Representative photomicrographs of the experimental sites are shown in Figs 3–6. The qualitative histologic observations are summarized in Table 1. An epithelial and connective tissue attachment appeared significantly extended in sites receiving rhPDGF/β-TCP compared with that of sites receiving rhGDF-5/β-TCP. The root surfaces were covered with cellular and/or acellular cementum in the rhGDF-5/β-TCP sites and predominantly acellular cementum in the rhPDGF/β-TCP sites. Cementum included a perpendicularly/obliquely oriented periodontal ligament (mixed fibre cementum) for both treatments. Periodontal ligament fibre density varied along the root surface with no apparent preference with regard to location. The functionally oriented fibres appeared of moderate density in most sections. Functionally oriented fibres did not only traverse the periodontal ligament space but were also observed supracrestally. Regenerated cementum generally extended above the alveolar crest for both treatments.

Newly formed alveolar bone varied in extension along the root surfaces in the rhGDF-5/β-TCP and the rhPDGF/β-TCP groups. Sites receiving rhGDF-5/β-TCP showed enhanced bone formation compared with sites receiving rhPDGF/β-TCP. Bone formation in rhGDF-5/β-TCP- treated defects appeared mostly lamellar with primary osteons in contrast to lamellar and woven bone in rhPDGF/β-TCP-treated defects. Sites treated with rhGDF-5/β-TCP showed more bone/osteoid formation on the surface of resolving β-TCP particles than that observed in sites treated with rhPDGF/β-TCP. One defect receiving rhGDF-5/β-TCP exhibited ankylosis. Residual β-TCP particles undergoing resorption were observed for both treatments; the β-TCP biomaterial exhibited timely resorption without appreciably affecting bone formation.

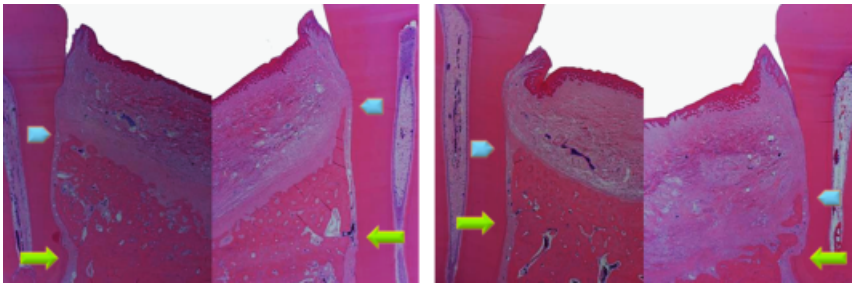

Fig. 3. Representative photomicrographs from contralateral jaw quadrants at 8 weeks following placement of rhGDF-5/β-TCP (left; fourth and second pre-molar sites) and rhPDGF/β-TCP (right; fourth and second pre-molar sites). Green arrows delineate the apical extension of the defects, the blue arrows the coronal extension of newly formed bone. Sites receiving rhGDF-5/β-TCP show significantly increased bone formation in comparison. Haematoxylin and eosin, original magnification × 10.

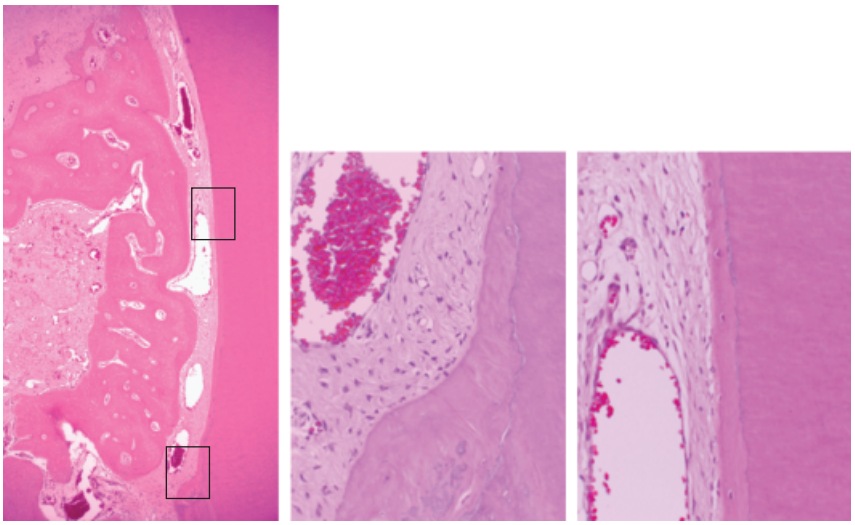

Fig. 4. Representative photomicrographs from site receiving rhGDF-5/β-TCP, overview and magnifications from the apical and more coronal aspects of the defect. A large amount of new bone and cementum formation is observed with a number of blood vessels in the periodontal ligament space (left). Thick and newly formed cementum is formed over the apical extension of root instrumentation (centre). Newly formed cellular cementum is observed along the instrumented root surface further coronally (right). Haematoxylin and eosin, original magnification × 40 and × 200.

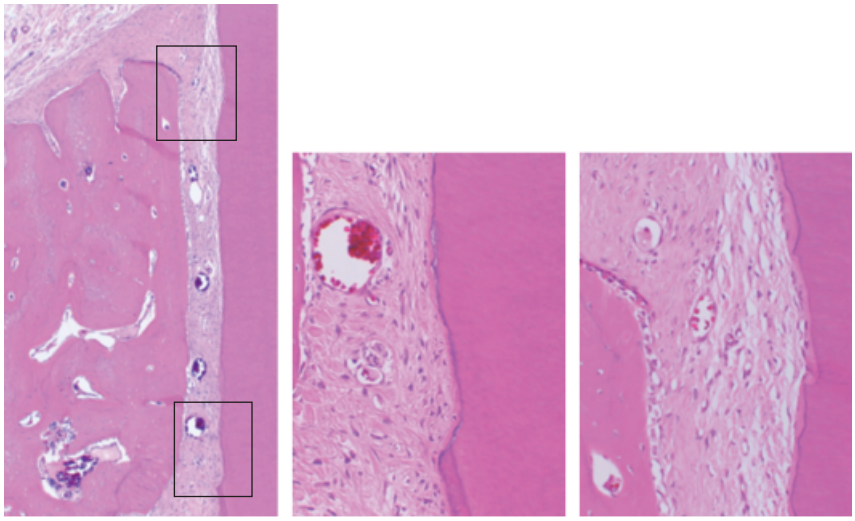

Fig. 5. Representative photomicrographs from site receiving rhPDGF/β-TCP, overview and magnifications from the apical and more coronal aspects of the defect. A large amount of new bone and cementum is formed and blood vessels are observed in the periodontal ligament space (left). Newly formed thin cementum is noted over the apical end of root instrumentation (centre). Acellular cementum is formed over the instrumented root surface (right). Haematoxylin and eosin, original magnification × 40 and × 200.

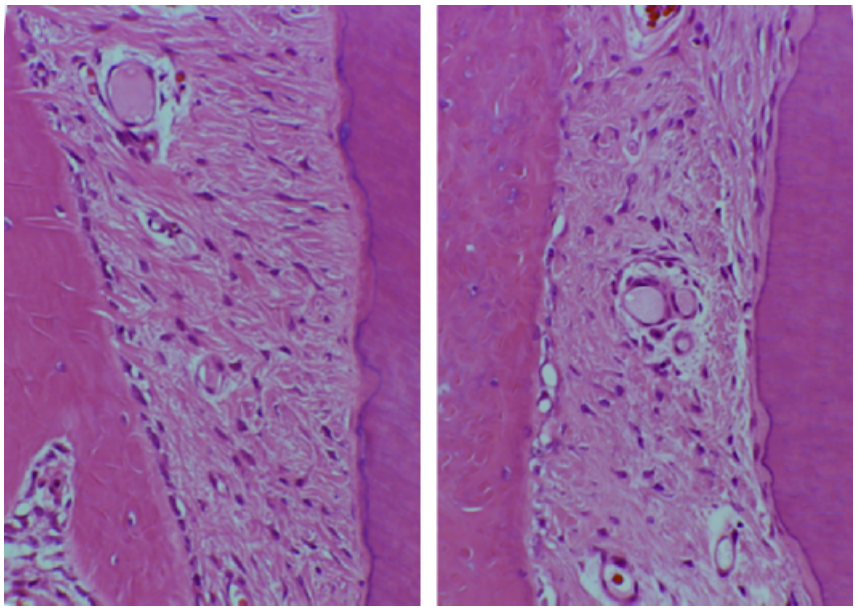

Fig. 6. Representative photomicrographs of the newly formed periodontal ligament for sites receiving rhGDF-5/β-TCP (left) and rhPDGF/β-TCP (right). Numerous osteoblasts are aligned along the newly formed bone, and new cementum is observed over the root surface with well-organized perpendicularly/obliquely oriented ligament fibres (left). A newly formed periodontal ligament is observed between new bone and new cementum along the root surface (right). Haematoxylin and eosin, original magnification × 200.

There were no remarkable inflammatory lesions in sites implanted with rhGDF-5/β-TCP or rhPDGF/β-TCP.

Histomorphometric analysis

The results of the histomorphometric analysis are shown in Table 2. Defect height averaged (± SD) 5.16 ± 0.43 *versus* 5.15 ± 0.17 mm for the rhGDF-5/β-TCP and rhPDGF/β-TCP groups, respectively ($p > 0.05$). Cementum regeneration averaged 4.49 ± 0.48 *versus* 2.72 ± 0.91 mm for the rhGDF-5/β-TCP and rhPDGF/β-TCP groups, respectively ($p < 0.001$). The corresponding values for bone regeneration height and area were 3.08 ± 0.74 mm and 6.03 ± 1.18 mm^2 *versus* 1.29 ± 0.78 mm and 2.98 ± 2.61 mm^2 ($p < 0.001$ and < 0.01, respectively). The epithelial attachment averaged 0.52 ± 0.40 *versus* 1.17 ± 0.52 mm for rhGDF-5/β-TCP and rhPDGF/β-TCP groups, respectively ($p < 0.04$). The corresponding values for the connective tissue attachment was 0.14 ± 0.25 and 1.25 ± 0.84 mm ($p < 0.001$).

Discussion

The objective of this study was to compare the effect of rhGDF-5 coated onto a bioresorbable granular β-TCP biomaterial (rhGDF-5/β-TCP) with a benchmark product, rhPDGF/β-TCP, on periodontal wound healing/regeneration using an established one-wall intrabony periodontal defect model, a Beagle dog platform, and an 8-week healing interval. The candidate rhGDF-5/β-TCP treatment concept showed significant superiority over the rhPDGF/β-TCP benchmark for all criteria relevant to periodontal wound healing/regeneration in this comparison.

The one-wall intrabony periodontal defect model has been shown to be a discriminating animal model for candidate regenerative therapies and has been used primarily for constructs that do not sustain compression from adjoining mucosal tissues or forces translated through these tissues, or constructs without corporal integrity such as the herein evaluated granular rhGDF-5/β-TCP and rhPDGF/β-TCP biomaterials (Kim et al. 2004, 2005). Transgingival wound closure allows near-clinical conditions evaluating the potential of a candidate material to stabilize the wound during the early healing sequence. An 8-week healing interval is used to allow tissue maturation that the periodontal attachment can be conveniently evaluated using routine incandescent and polarized light microscopy. In the present study, the 8-week healing interval allowed evaluation of accelerated wound healing/maturation comparing experimental and benchmark treatments.

Cementum regeneration was significantly enhanced in sites receiving the candidate rhGDF-5/β-TCP treatment compared with the rhPDGF/β-TCP benchmark, and comparable with that reported from a parallel study evaluating rhGDF-5/β-TCP *versus* β-TCP and

Table 1. Frequency of main qualitative histologic observations

	Bone		Residual biomaterial	Cementum					Fibre density
	lamellar	woven		cellular	acellular	intrinsic	extrinsic	mixed	
rhGDF-5/β-TCP									
Animals	5/5	0/5	5/5	3/5	2/5	1/5	0/5	5/5	2.4
Sites	9/9	0/9	7/9	6/9	3/9	1/9	0/9	8/9	
rhPDGF/β-TCP									
Animals	4/5	4/5	5/5	1/5	5/5	0/5	0/5	5/5	2.5
Sites	4/8	4/8	10/10	1/10	9/10	0/10	0/10	8/8	

rhGDF-5/β-TCP: root resorption/ankylosis 1/5 animals 1/10 sites.
rhGDF-5, recombinant human growth/differentiation factor-5; β-TCP, β-tricalcium phosphate.

Table 2. Histometric analysis of periodontal wound healing/regeneration following surgical implantation of rhGDF-5/β-TCP *versus* rhPDGF/β-TCP in one-wall intrabony periodontal defects in dogs (means ± SD in mm/mm^2)

	Defect height	Epithelial attachment	Connective tissue attachment	Cementum regeneration	Bone regeneration (height)	Bone regeneration (area)
rhGDF-5/β-TCP	5.16 ± 0.43	0.52 ± 0.40	0.14 ± 0.25	4.49 ± 0.48	3.08 ± 0.74	6.03 ± 1.18
rhPDGF/β-TCP	5.15 ± 0.17	1.17 ± 0.52	1.25 ± 0.84	2.72 ± 0.91	1.29 ± 0.78	2.98 ± 2.61
p-value	> 0.05	**< 0.04**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.01**

Bold values is used to emphasize statistically significant results.
rhGDF-5, recombinant human growth/differentiation factor-5; β-TCP, β-tricalcium phosphate.

sham surgery controls (Lee et al. 2010). In dogs, native unabated periodontal regeneration includes the formation of a cellular extrinsic/mixed fibre cementum gradually thinning in a coronal dimension within an 8-week healing interval as has been shown using the critical-size supraalveolar periodontal defect model (Sigurdsson et al. 1994, Wikesjö et al. 2003b, c). Native cementum regeneration appears less developed following a 4-week healing interval (Haney et al. 1993, Wikesjö et al. 1998, 2003a). A gradually thinner cellular mixed fibre cementum covered almost the complete experimental defect in sites receiving rhGDF-5/β-TCP *versus* the limited apparently thinner, acellular cementum following application of rhPDGF/β-TCP. The apparently thinner, acellular cementum in sites receiving rhPDGF/β-TCP may perhaps be a reflection of delayed tissue maturation. Longer observation periods may be useful to clarify this inconsistency in cementum regeneration between the candidate rhGDF-5/β-TCP and rhPDGF/β-TCP benchmark treatments.

The newly formed or regenerated periodontal ligament did not particularly differ between sites receiving rhGDF-5/β-TCP and the rhPDGF/β-TCP benchmark; the perpendicularly/obliquely oriented periodontal attachment being of moderate density for both treatments. Functionally oriented fibres did not only traverse the periodontal ligament space but were also observed supracrestally. These observations are consistent with observations from previous studies evaluating rhGDF-5 and rhGDF-7 (rhBMP-12) in an absorbable collagen sponge carrier (Wikesjö et al. 2004, Kim et al. 2009), however, in stark contrast to rhBMP-2 at various dosages and a multiple of carrier technologies using comparable models and healing intervals (Sigurdsson et al. 1994, 1996, Choi et al. 2002, Selvig et al. 2002, Wikesjö et al. 1999, 2003b, d, e, 2004, Sorensen et al. 2004). Whereas rhGDF-7 might support and even accelerate the innate regenerative potential of the periodontal attachment, the bone inductive capacity of rhBMP-2 produced a fibrovascular tissue without an appreciable periodontal ligament that eventually morphs into root resorption/ankylosis (Wikesjö et al. 2003b).

Bone formation in rhGDF-5/β-TCP-treated defects appeared mostly lamellar with primary osteons in contrast to lamellar and woven bone in rhPDGF/β-TCP-treated defects suggesting that the rhGDF-5/β-TCP construct accelerated bone maturation. Moreover, bone formation (area/height) was significantly enhanced (2–2.5 times) in sites receiving rhGDF-5/β-TCP compared with the rhPDGF/β-TCP benchmark emphasizing a significant regenerative potential of the candidate rhGDF-5/β-TCP construct. A similar regenerative potential of the rhGDF-5/β-TCP candidate treatment has been shown comparing rhGDF-5/β-TCP with β-TCP and sham-surgery controls also using the one-wall intrabony periodontal defect model; the β-TCP and sham-surgery controls exhibited a regenerative potential similar to that of the rhPDGF/β-TCP benchmark in the present study (Lee et al. 2010). The observation that sites treated with rhGDF-5/β-TCP showed more bone/osteoid formation than that observed in sites treated with rhPDGF/β-TCP appears consistent with an overall enhanced, accelerated bone formation following the use of rhGDF-5/β-TCP. Even though the morphologic characteristics of β-TCP were slightly different, apparently the β-TCP biomaterials exhibit a timely biodegradation profile that does not substantially interfere with bone formation as has been shown for other bone biomaterials used to support combination products including rhBMP-2 and a prostaglandin E_1 analogue (Sigurdsson et al. 1996, Trombelli et al. 1999).

One site receiving rhGDF-5/β-TCP exhibited limited ankylosis. A 24-week healing interval, not included in the present study, is used to ensure the stability of the regenerated tissues so that tissue maturation does not morph into root resorption/ankylosis. Although incidental root resorption/ankylosis may be observed in most animal models, systematic observations raise concern relative the usefulness of a treatment

concept in clinical settings. In perspective, incidental ankylosis has been observed following guided tissue regeneration (GTR) using the critical-size supraalveolar periodontal defect model (Sigurdsson et al. 1994); however, root resorption/ankylosis has not been an impediment when GTR has been applied in clinical settings. In perspective, side-by-side evaluations of GTR and rhBMP-2 in a hyaluronan carrier disclosed a significant propensity for the rhBMP-2/hyaluronan combination to induce root resorption/ankylosis within an 8-week interval, which was substantiated using a 24-week healing interval (Wikesjö et al. 2003b). Unpublished observations from evaluations using the one-wall intrabony periodontal defect model and a 24-week healing interval suggest that the rhGDF-5/β-TCP candidate treatment is not associated with root resorption/ankylosis.

Conclusion

Within the limitation of this study, it may be concluded that rhGDF-5/β-TCP supports/accelerates periodontal wound healing/regeneration in advanced periodontal defects. rhGDF-5/β-TCP appears safe and thus appears as a lead candidate for clinical evaluation.

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Clinical Relevance

Scientific rationale for the study: rhGDF-5 in a β-TCP carrier has been shown to enhance regeneration in advanced periodontal defects over β-TCP carrier and sham-surgery controls. The objective of this study was to benchmark the regenerative potential of the rhGDF-5/β-TCP candidate treatment to that of a commercially available technology based on an rhPDGF/β-TCP composite.

Principal findings: Surgical implantation of rhGDF-5/β-TCP resulted in significantly enhanced periodontal regeneration compared with the rhPDGF/β-TCP benchmark. The rhGDF-5 and rhPDGF treatments were not associated with root resorption/ankylosis or other aberrant tissue reactions.

Practical implications: This study indicates that rhGDF-5/β-TCP may be used safely and effectively to support wound healing/regeneration in periodontal defects.