REVIEW ARTICLE

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Bone morphogenetic proteins for periodontal and alveolar indications; biological observations – clinical implications

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Structured Abstract

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Surgical placement of endosseous oral implants is governed by the prosthetic design and by the morphology and quality of the alveolar bone. Nevertheless, often implant placement may be complexed, if at all possible, by alveolar ridge irregularities resulting from periodontal disease, and chronic and acute trauma. In consequence, implant positioning commonly necessitates bone augmentation procedures. One objective of our laboratory is to evaluate the biologic potential of bone morphogenetic proteins (BMP) and other candidate biologics, bone biomaterials, and devices for alveolar ridge augmentation and implant fixation using discriminating large animal models. This focused review illustrates the unique biologic potential, the clinical relevance and perspectives of recombinant human BMP-2 (rhBMP-2) using a variety of carrier technologies to induce local bone formation and implant osseointegration for inlay and onlay indications. Our studies demonstrate a clinically relevant potential of a purpose-designed titanium porous oxide implant surface as stand-alone technology to deliver rhBMP-2 for alveolar augmentation. In perspective, merits and shortcomings of current treatment protocol including bone biomaterials and guided bone regeneration are addressed and explained. We demonstrate that rhBMP-2 has unparalleled potential to augment alveolar bone, and support implant osseointegration and long-term functional loading. Inclusion of rhBMP-2 for alveolar augmentation and osseointegration will not only enhance predictability of existing clinical protocol but also radically change current treatment paradigms.

Key words: bone formation; bone morphogenetic protein; osseointegration; tissue engineering; titanium implants

Introduction: the search for safe and effective therapies for alveolar bone augmentation

An abundance of surgical techniques and technologies aiming at bone augmentation and osseointegration of prosthetic implants in the axial and appendicular skeleton are continuously introduced. Thus, orthopedic,

oral/maxillofacial, and periodontal surgeons often confront the dilemma of selecting one technology or therapy over the other. The decision-making process becomes delicate when one considers that often the scientific support is limited, that evidence-based evaluations are rare; pre-clinical data often restricted to *in vitro* and small animal (rodent) model observations rarely corroborated using discriminating large animal critical-size models for clinical relevance; and supporting pivotal clinical evaluations often focusing on statistical significance rather than clinically relevant statistically significant effects. The objective of this focused review is to present pre-clinical evidence, and in perspective the clinical relevance, for the use of bone morphogenetic protein (BMP) technologies for alveolar bone augmentation and endosseous implant osseointegration.

Discovery and development

Ever since the discovery, eventual purification, cloning, and characterization of BMPs (1–9), treatment concepts including purified or recombinant BMPs have been evaluated in support of bone formation including orthopedic and oral indications (10–12). Several studies in pre-clinical and clinical settings have concerned alveolar augmentation/endosseous implant osseointegration following surgical implantation of in particular recombinant human BMP-2 (rhBMP-2), rhBMP-7 [also known as recombinant human osteogenic protein-1 (rhOP-1)], and recombinant human growth/differentiation factor-5 (rhGDF-5) [also known as recombinant human cartilage derived morphogenetic protein-1 (rhCDMP-1)] combined with a variety of candidate biomaterials used as delivery systems (13).

Conditions for pre-clinical evaluation

Development of safe and effective therapies for alveolar augmentation requires pre-clinical evaluation to estimate biologic potential, efficacy, and safety prior to clinical introduction. Well-characterized rodent *screening models* are initially used to assess biologic potential and safety. Therapies thus exhibiting biologic potential and safety should then be evaluated for clinical potential and efficacy in discriminating pre-clinical models often designated as *critical-size defect models* using relevant alveolar settings in large animals including canines or non-human primates. Critical-size defects are defects that must not spontaneously regenerate following reconstructive surgery without adjunctive measures. Critical-size defects must also allow clinically relevant bone formation induced or supported by implanted biologics, biomaterials, or devices over that in a surgical control. Our laboratory has developed and characterized a *Critical-size Supraalveolar Periodontal Defect Model* (14). This model has proven to be a 'litmus test' for candidate therapies for periodontal regeneration. We subsequently modified this defect model to study of regeneration of alveolar bone and osseointegration of endosseous oral implants introducing a *Critical-size Supraalveolar Peri-Implant Defect Model* (Fig. 1; 15).

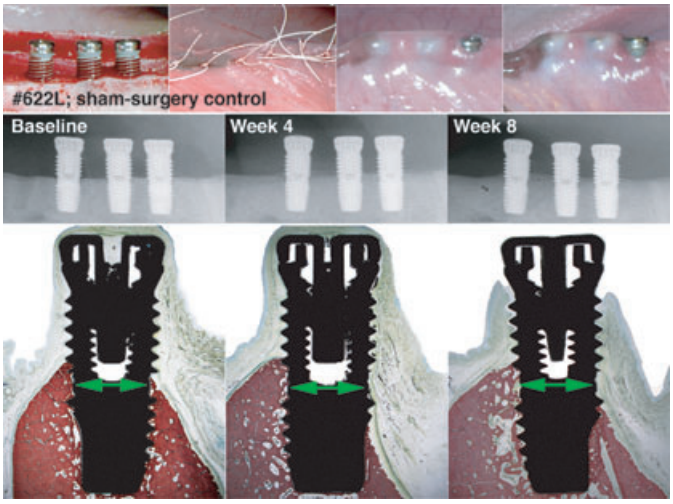

Fig. 1. Clinical, radiographic, and histologic representation of the *Critical-size Supraalveolar Peri-Implant Defect Model.* Clinical panels show implant placement, wound closure, and healing at week 4 and 8. Three ø4.0 × 10 mm implants are placed 5 mm into osteotomies prepared into the extraction sites of the mandibular third and fourth premolar teeth immediately following surgical reduction of the alveolar bone, extraction of the mandibular premolars, and amputation of the first mandibular molar leaving 5 mm of the implant in a supra-alveolar position. The implant platforms (cover screws) can be visualized through the mucosa at week 4 and 8 when one implant becomes exposed. Radiographs show limited, if any, new bone formation. The photomicrographs show limited bone formation confined to the lingual aspect of the implants whereas the buccal aspect shows loss of crestal bone. Green arrows delineate a 5-mm notch placed level with the resident alveolar bone. From references 15 and 33; Figure copyrighted by Wiley-Blackwell, reprinted with permission.

Orthotopic bone formation – osseointegration

Sigurdsson et al. (16) using the critical-size supraalveolar peri-implant defect model first established that rhBMP-2 (Wyeth Research, Cambrige, MA, USA) in a carrier induced significant alveolar bone augmentation (Fig. 2). rhBMP-2 (0.4 mg/ml) in an absorbable collagen sponge (ACS) carrier or buffer/ACS (control) were implanted into contralateral peri-implant defects in five Beagle dogs. Block biopsies for the histometric evaluation were collected following a 16-week healing interval. Defect sites implanted with rhBMP-2/ACS exhibited significant, clinically relevant, vertical alveolar augmentation compared with control (4.2 ± 1.0 mm vs. 0.5 ± 0.3 mm, $p < 0.002$). The newly formed bone exhibited osseointegration to the titanium implant, however, bone-implant contact was, as could be expected, lower than that in resident bone following the short healing interval. Notably, induced bone often constituted only a thin layer on the implant surface. Evidently, the ACS was ineffective in predictably providing adequate space for rhBMP-2-induced bone formation.

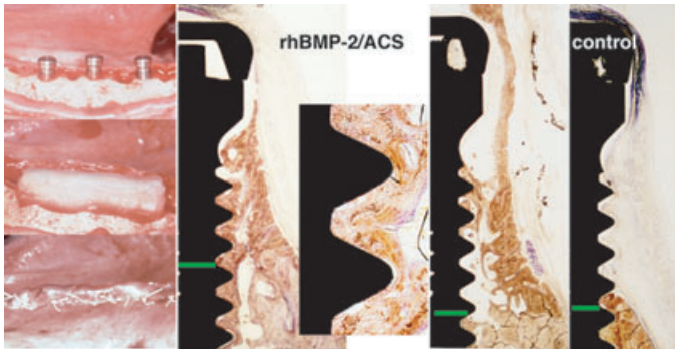

Fig. 2. Critical-size, supraalveolar, peri-implant defect implanted with rhBMP-2/absorbable collagen sponge (ACS) or ACS without rhBMP-2 (control). Clinical panels show the supraalveolar defect with rhBMP-2/ACS before and after wound closure for primary intention healing. The photomicrographs show defect sites implanted with rhBMP-2/ACS exhibiting bone formation reaching or exceeding the implant plat form, the newly formed bone showing osseointegration to the machined titanium implant surface (high magnification insert). Control sites show limited, if any, bone formation. Green lines delineate the level of the surgically reduced alveolar crest. Healing interval 16 weeks. From reference 16; Figures copyrighted by and modified with permission from Wiley-Blackwell.

The observations from Sigurdsson et al. (16) become even more conspicuous when compared with that following guided bone regeneration (GBR) and GBR combined with an allogeneic, freeze-dried, decalcified bone (DFDBA) biomaterial in the critical-size supraalveolar peri-implant defect model, both treatment concepts widespread in clinical practice (17). Contralateral supraalveolar peri-implant defects in five Beagle dogs received a space-providing, occlusive, expanded polytetrafluoroethylene (ePTFE) GBR device (W.L. Gore & Associates Inc., Flagstaff, AZ, USA) and DFDBA rehydrated in autologous blood, or received the GBR device solo. Block biopsies for histometric analysis were collected following a 16-week healing interval (Fig. 3). The DFDBA biomaterial was discernible in all sites receiving this treatment. DFDBA particles appeared solidified within a dense connective tissue matrix and in close contact to the titanium implant surface without evidence of osseointegration. Vertical alveolar ridge augmentation was limited averaging 1.5 ± 0.9 mm for the GBR/DFDBA combination and 1.1 ± 0.4 mm for GBR solo. There were no significant or

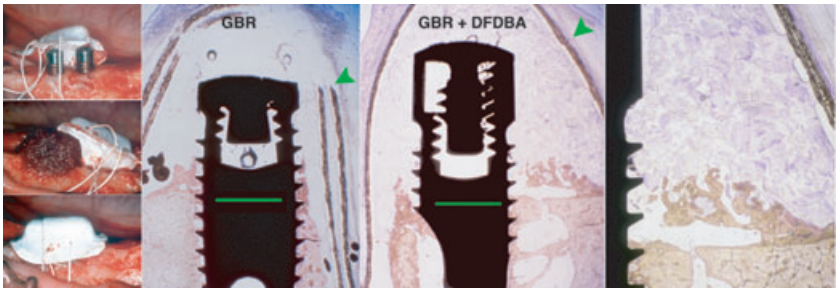

Fig. 3. Critical-size, supraalveolar, peri-implant defect treated with guided bone regeneration (GBR), using an occlusive space-providing expanded polytetrafluoroethylene device (green arrowheads), with or without a decalcified freeze-dried bone biomaterial (DFDBA). Clinical panels show the supraalveolar defect with the GBR device, with DFDBA rehydrated in autologous blood, and with the device in place prior to wound closure for primary intention healing. Note limited regeneration of alveolar bone in absence and presence of DFDBA suggesting that the innate regenerative potential of alveolar bone is limited, and that the DFDBA biomaterial has limited, if any, osteoinductive and/or osteoconductive properties to support bone regeneration. Green lines delineate the level of the surgically reduced alveolar crest. Healing interval 16 weeks. From reference 17; Figures copyrighted by and modified with permission from Quintessence Publishing.

meaningful differences between experimental conditions for any parameter examined. Notably, physiologic concentrations of bone growth factors sequestered in DFDBA had no relevant effect on alveolar bone formation given that the DFDBA particles were invested in fibrous connective tissue without apparent evidence of bone metabolic activity. These observations suggest that DFDBA has no relevant osteoinductive, osteoconductive, or other adjunctive effect to GBR and that GBR therapy has limited potential to augment alveolar bone at least when used for onlay indications.

In following, we evaluated a space-providing macro-porous (ePTFE) GBR device to support rhBMP-2/ACS-induced (Wyeth Research) bone formation using the critical-size supraalveolar peri-implant defect model. The GBR device was designed to preclude compression of the rhBMP-2/ACS construct while allowing vascularity from the gingival connective tissue to support rhBMP-2-induced bone formation (Fig. 4; 18, 19). Eight Hound-Labrador mongrel dogs were used; four animals received GBR alone vs. rhBMP-2(0.4 mg)/ACS combined with GBR in contralateral supraalveolar peri-implant defects, and four animals received rhBMP-2(0.4 mg)/ACS alone vs. rhBMP-2(0.4 mg)/ACS combined with GBR. Block biopsies for histometric analysis were collected following an 8-week healing interval. Corroborating Caplanis et al. (17), this study showed that GBR limitedly enhanced bone formation, vertical bone gain averaging 1.8 ± 2.0 mm and new bone area 1.8 ± 1.3 mm^2 at the turned implants (19). Corroborating Sigurdsson et al. (16) and Tatakis et al. (20), jaw quadrants implanted with rhBMP-2/ACS solo showed significant augmentation of the alveolar ridge; however, the geometry of induced bone was highly irregular; vertical bone gain at turned implants averaging 3.5 ± 0.9 mm and induced bone area 7.5 ± 6.2 mm^2 (18). In contrast, the GBR-rhBMP-2/ACS combination predictably resulted in bone formation filling the dome-shaped GBR device; vertical bone gain at turned implants averaging 4.7 ± 0.2 mm and induced bone area 9.6 ± 0.7 mm^2 generating a highly significant correlation between induced bone area and the space provided by the GBR device ($p < 0.001$; 18). The newly formed bone provided osseointegration with minor unremarkable differences between turned and acid-etched titanium endosseous implants (21). This study provides an important insight in tissue engineering principles using BMP; that space-provision appears critical to draw clinically significant benefits from a BMP construct.

Still other studies further demonstrate the significant clinical utility of rhBMP-2/ACS using pre-clinical settings. rhBMP-2/ACS has been shown to induce significant bone formation to: 1) place endosseous oral implants in the edentulous posterior maxilla using a

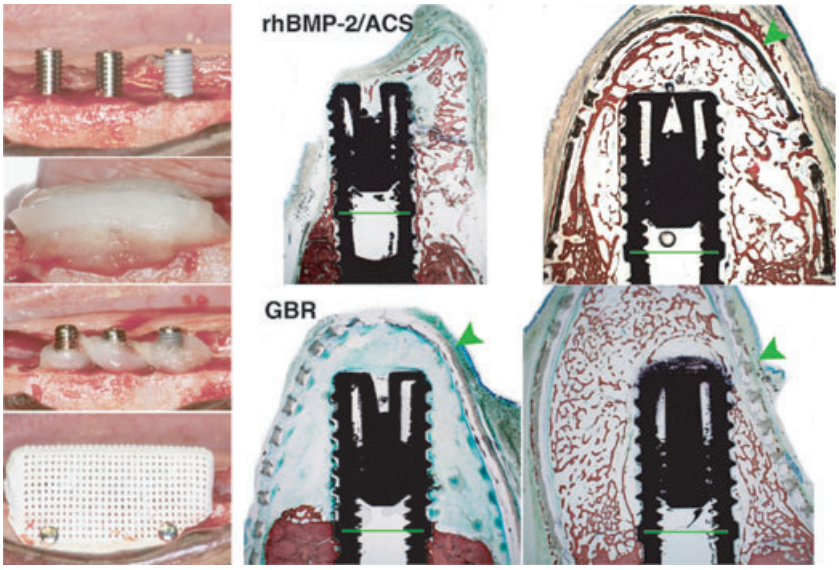

Fig. 4. Critical-size, supraalveolar, peri-implant defects treated with rhBMP-2/absorbable collagen sponge (ACS), guided bone regeneration (GBR), or rhBMP-2/ACS combined with GBR using a porous, space-providing expanded polytetrafluoroethylene device. The clinical panels show the supraalveolar defect with rhBMP-2/ACS and with the porous GBR membrane. Note how rhBMP-2-induced bone fills the space provided by the membrane (green arrowheads) whereas rhBMP-2/ACS alone provides very irregular bone formation (top left). GBR alone (bottom left) provides limited, if any, regeneration of alveolar bone. Green lines delineate the level of the surgically reduced alveolar crest. Healing interval 8 weeks. From references 18 and 19; Figures copyrighted by and modified with permission from Wiley-Blackwell.

Cynomolgus monkey model (22); 2) resolve chronic peri-implantitis defects including re-established osseointegration using a Cynomolgus monkey model (23, 24); and 3) augment significant saddle-type intrabony defects (25–27) to allow placement and osseointegration of endosseous oral implants subject to long-term (12-month) functional loading (26) using a canine model.

Alternative carrier technologies

Alternative carrier technologies to ACS exhibiting structural integrity have been evaluated. Sigurdsson et al. (28) showed that rhBMP-2 in a DFDBA/fibrin carrier might have substantial clinical utility to augment difficult to treat alveolar ridge defects applying rhBMP-2(0.2 mg/ml)/DFDBA/fibrin onlays onto surgically created horizontal alveolar defects in five Beagle dogs (Fig. 5). Ten-mm, endosseous oral implants were placed into the rhBMP-2-induced alveolar ridge at 8 and 16 weeks. Block biopsies for histometric analysis were collected at 24 weeks. Roughly 90% of the implant bone-anchoring surfaces were invested in rhBMP-2-induced bone leaving not more than the apex of the implants interfacing resident bone. Similar levels of bone-implant contact (~55%) were observed in rhBMP-2-induced and resident bone irrespective of osseointegration interval (8 or 16 weeks). There was no significant difference in bone density between rhBMP-2-induced and resident bone. Nevertheless, the use of cadaver-derived biomaterials such as DFDBA may have difficulty to receive public acceptance for elective procedures thus synthetic carrier technologies for alveolar indications need to be explored.

In a subsequent study, our laboratory demonstrated the efficacy of a synthetic calcium–phosphate cement carrier (α-BSM®; ETEX Corp., Cambridge, MA, USA) as a candidate carrier for rhBMP-2 using the critical-size supraalveolar peri-implant defect model applied to six adult Hound Labrador mongrel dogs (Fig. 6; 29). Three animals received rhBMP-2/α-BSM® (0.40 and 0.75 mg/ml) in contralateral jaw quadrants and three animals received α-BSM® without rhBMP-2 (control). Block biopsies for histometric analysis were collected following a 16-week healing interval. rhBMP-2/α-BSM®-induced substantial, clinically relevant, augmentation of the alveolar ridge while control sites exhibited limited, if any, new bone formation. Vertical bone formation comprised almost the entire 5-mm exposed implants, the newly formed bone exhibiting bone density approximating 60% (Type II bone) with established cortex and bone-implant contact approximating 27%. Clearly, this novel technology shows considerable promise for a number of indications since α-BSM® may conveniently be shaped to desired contour and sets to resist compression to provide space for rhBMP-2-induced bone formation. In addition, α-BSM® is injectable for ease-of-use application and may well prove to be a remarkable technology for augmentation of the maxillary sinus in conjunction with placement of endosseous oral implants predictably pin-pointing bone formation at the implant body using either a lateral or immediate alveolar approach.

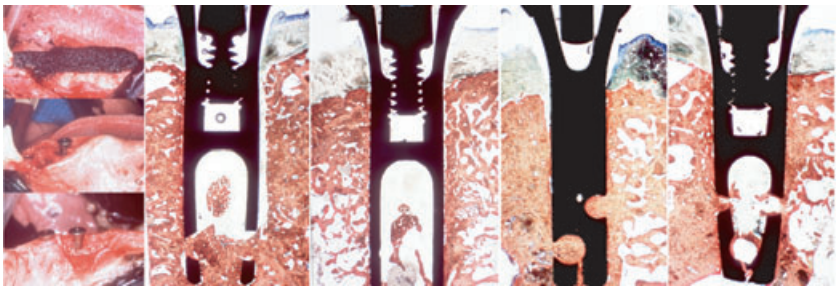

Fig. 5. Surgically created horizontal alveolar ridge defect implanted with rhBMP-2 combined with decalcified freeze-dried bone biomaterial rehydrated in autologous blood. Clinical panels show the rhBMP-2 construct placed onto the surgically reduced alveolar ridge prior to wound closure for primary intention healing. Endosseous oral implants were placed into the rhBMP-2-induced alveolar ridge at week 8 and 16. The animals were euthanized at week 24. Left and right photomicrographs show implants placed at week 8 and 16, respectively. Approximately 90% of the bone-anchoring surface of the implants was housed in rhBMP-2-induced bone exhibiting limited evidence of crestal resorption. There was no significant difference in bone density between rhBMP-2-induced and the contiguous resident bone. Also osseointegration (approximately 55%) was similar in induced and resident bone irrespective of whether the implants were placed at week 8 or 16. From reference 28; Figures copyrighted by and modified with permission from Quintessence Publishing.

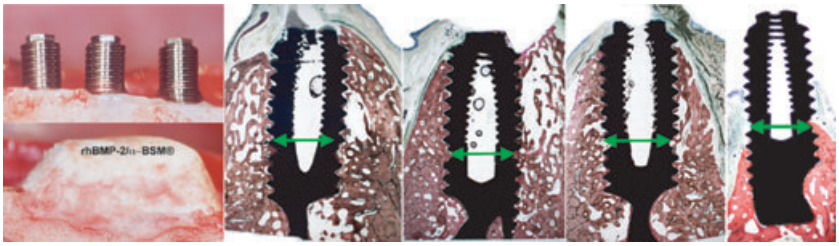

Fig. 6. Critical-size, supraalveolar peri-implant defect treated with rhBMP-2 in a calcium phosphate cement (α-BSM®) or α-BSM® without rhBMP-2 (control). Clinical panels show the supraalveolar peri-implant defect before and after application of α-BSM®. Photomicrographs show representative observations for jaw quadrants receiving rhBMP-2/α-BSM®, in this particular jaw quadrant rhBMP-2 at 0.4 mg/ml. Note substantial new bone formation at sites treated with rhBMP-2/α-BSM® compared with the control (far right) exhibiting limited, if any, evidence of new bone formation. The rhBMP-2-induced bone exhibits similar trabeculation, osseointegration, and cortex formation as the contiguous resident bone. Also note no evidence of residual biomaterial. Green arrows delineate the apical extension of the supraalveolar peri-implant defects. Healing interval 16 weeks. From reference 29; Figures copyrighted by and modified with permission from Wiley-Blackwell.

Development of a bone-inductive oral implant

Hypothetically, orthopedic and oral implants coated with a bone inductive factor such as a BMP may stimulate local bone formation and osseointegration in sites of poor bone quality or in need of augmentation. In a step-wise progression using rodent ectopic, and canine and non-human primate orthotopic models we investigated a concept of applying rhBMP-2 onto purpose-designed implant surfaces (Nobel Biocare AB, Göteborg, Sweden) for enhanced local bone formation (30–33). Using a rat ectopic screening model, titanium disks exhibiting titanium porous oxide and turned (control) surfaces coated with rhBMP-2 were implanted into the ventral thoracic region (30). Biopsies for histometric analysis were collected following a 14-day healing interval. All surface technologies coated with rhBMP-2 showed significant bone formation and bone-implant contact; a titanium porous oxide surface with open pores appearing the most effective surface. Subsequently, screw-type endosseous oral implants with the titanium porous oxide surface with open pores coated with rhBMP-2 were implanted into the edentulated posterior mandible in dogs (Type II bone) using an 8-week healing interval (31), and into the edentulated posterior maxilla in the Cynomolgus monkey (Type IV bone) using a 16-week healing interval (32). A high and a low rhBMP-2 concentration (canine study: 0.2 and 4.0 mg/ml; non-human primate study: 0.2 and 2.0 mg/ml) were used. Implants coated with rhBMP-2 exhibited accelerated local bone formation in a dose-dependent order. In following, the rhBMP-2-coated endosseous oral implants were evaluated using the critical-size supraalveolar peri-implant defect model in twelve young adult Hound Labrador mongrel dogs (33). Six animals received implants coated with rhBMP-2 at 0.75 or 1.5 mg/ml; and six animals implants coated rhBMP-2 at 3.0 mg/ml or uncoated control. Block biopsies for histometric analysis were collected following an 8-week healing interval. The histologic evaluation showed robust bone formation reaching or exceeding the implant platform (Fig. 7). The newly formed bone exhibited characteristics of the adjoining resident Type II bone including cortex formation for sites using implants coated with rhBMP-2 at 0.75 or 1.5 mg/ml. Sites using implants coated with rhBMP-2 at 3.0 mg/ml exhibited immature trabecular bone formation, seroma formation, and peri-implant bone

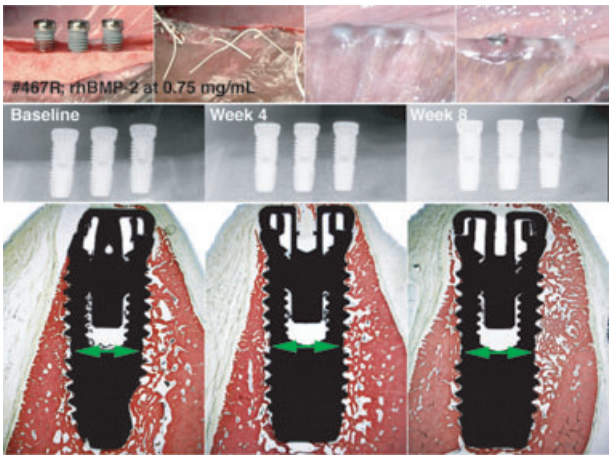

Fig. 7. Clinical panels show ø4.0 × 10 mm implants coated with rhBMP-2 at 0.75 mg/ml following placement and wound closure, and healing at week 4 and 8. The implant platforms (cover screws) can be visualized through the mucosa at week 4 and 8 when one implant becomes exposed. Radiographs show bone formation reaching the implant platform at week 4 and 8. Photomicrographs show bone formation with an established cortex reaching or exceeding the implant platform. Green arrows delineate a 5-mm notch placed level with the resident alveolar bone. From reference 33; Figure copyrighted by Wiley-Blackwell, reprinted with permission.

remodeling sometimes resulting in undesirable displacement (33, 34). Control implants exhibited minimal, if any, bone formation. All groups exhibited clinically relevant osseointegration. Collectively, these studies using ectopic and orthotopic small and large animal models demonstrate that rhBMP-2 can be delivered successfully to induce local bone formation and osseointegration using the titanium porous oxide surface as a carrier.

Conclusions

Pre-clinical studies have shown that rhBMP-2 induces normal physiologic bone in clinically relevant defects in the craniofacial skeleton. The newly formed bone assumes characteristics of the adjoining resident bone and allows placement, osseointegration/re-osseointegration, and functional loading of titanium implants. Studies using the critical-size, supraalveolar peri-implant defect model show that purpose-designed implant surfaces coated with rhBMP-2 can re-establish the alveolar ridge resulting in formation of Type II bone and significant osseointegration without the adjunctive use of biomaterials or devices for GBR and may thus in itself represent a significant advancement in patient rehabilitation. Clinical studies optimizing dose, delivery technologies, and conditions for stimulation of bone growth will bring about a new epoch; the ability to predictably promote osteogenesis using BMP-technologies is becoming a clinical reality and will without doubt profoundly influence the practice of dentistry.

Clinical relevance

This focused review suggests that rhBMP-2 has an unparalleled potential to augment alveolar bone, and support implant osseointegration and long-term functional loading. Inclusion of rhBMP-2 for alveolar augmentation and osseointegration will not only enhance predictability of existing clinical protocol but also radically change current treatment paradigms.

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