Clinical investigation of rhBMP-2 and simultaneous Dental Implants Placement: preliminary results

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SUMMARY
Background. Rebuilding atrophied alveolar ridges can present a significant challenge. There is a multitude of treatment options including guided bone regeneration, onlay block grafting, and distraction osteogenesis. Positioning of dental implants can be placed in an immediate or delayed fashion. An advantage of placing implants immediately is that the patient's treatment course is shortened as well as the potential for maintaining soft tissue is present.
Methods. The recent FDA approval of recombinant human bone morphogenic protein (rhBMP-2) has given clinicians an added treatment option for reconstructing localized alveolar defects. Several patients have been treated with dental implant and rhBMP-2 and the results were recorded by clinical and radiological exams.
Results. The potential to reconstruct these challenging defects with a growth factor thus limiting or even avoiding a secondary harvest site is exciting. We describe our experience with the use of implants and bone morphogenic protein together. This study presents excellent results about the combination of using dental implants and growth factor for treating substantial bone defects.
Conclusion. Our goal was to clinically evaluate the potential of a purpose designed titanium porous-oxide dental implant surface combined with rhBMP-2.

Key words: recombinant human bone morphogenetic protein-2, dental implants.

Introduction

Several surgical techniques and technologies aiming at bone augmentation and osseointegration of prosthetic implants in the axial and body skeleton are continuously introduced. Thus, orthopaedic, oral/maxillofacial, and periodontal surgeons often confront the dilemma of selecting one technology or therapy over the other. In orthopaedic and dental implantology, novel tools and techniques are being sought to improve the regeneration of bone tissue. Numerous attempts have been made to enhance the osteoconductivity of titanium prostheses, including modifications in their surface properties and coating with layers of calcium phosphate (1-4). The decision-making process about the treatment choice for atrophic ridge reconstruction and dental implant positioning becomes difficult. The treatment of severe atrophies of the jaw is not so rare and clinicians had no references both for the surgical technique decision, and for the graft material choice.
The investigations supporting pivotal clinical evaluations often focus on the statistical significance rather than clinically relevant statistically significant effects of the biomaterials and surgi-

cal techniques. Moreover the pre-clinical data are usually referred to *in vitro* or clinical animal model observations (5-10). In the oral cavity and before dental implant positioning, the bone level constitutes the base for the soft tissue, and evidence supports the existence of a 'biological width' of the supra-crestal soft tissue around the implant similar to that defined for the natural tooth (11, 12). For this reason vertical and horizontal bone loss may negatively influence the soft tissue topography and compromise the aesthetic outcome of implant therapy (13). Thus, the placement of an implant in an extreme facial position may result not only in a bone dehiscence but also in a too thin supra-crestal mucosa. In the past 20 years, the number of dental implant procedures has increased steadily worldwide, reaching about one million dental implantations per year (14). The use of dental implants for the oral rehabilitation of fully and partially edentulous patients has greatly broadened the scope of clinical dentistry, creating additional treatment options in complex cases in which functional rehabilitation was previously limited or inadequate. The predictability and long-term success of dental implants have been well documented, both in removable and fixed prostheses (15).

The clinical success of oral implants is related to their early osseointegration. Geometry and surface topography are crucial for the short- and long-term success of dental implants (12-15). These parameters are associated with delicate surgical techniques, a prerequisite for successful early clinical outcome (16).

Several factors that could compromise implant success are well analyzed in the literature.

Factors such as material biocompatibility, implant design and surface, surgical technique, host bed, and the loading conditions have all been shown to influence the implant osseointegration. Moreover, the surface condition is not the only factor that could influence osseointegration. Implant design can affect surgical insertion (e.g. stability) and the bone-implant interface after occlusal loading. Implant design and surface conditions are independent conditions and can determine the implant success rates (17-19).

Dental implants, which may allow for optimal aesthetic and functional restoration, have been available for many years, but have not always been as convenient and accessible as at this time. In recent years, dental implant rehabilitation has faced demands from prosthetic and aesthetic arenas calling for increasingly ideal outcomes, which require precise surgical planning and placement. The osteoconductivity of titanium implants can be improved either if their surface properties are modified or if they are coated with a layer of calcium phosphate (19-21). Surgical placement of oral implants is primarily governed by the prosthetic design and, secondarily, by the morphology and quality of the alveolar bone. Implant placement, however, may at times be demanding, if at all possible, due to aberrations of the alveolar ridge.

Dr. Marshal Urist discovered a group of proteins sequestered in bone and aptly named them bone morphogenetic proteins. He observed that bone matrix preparations contained bone morphogenetic proteins that induced cartilage, bone, and marrow formation when implanted intramuscularly in rodent models (21-23). The bone morphogenetic proteins have been studied extensively and represent a significant addition to our understanding of bone biology and development. The influence of bone morphogenetic proteins may begin as early as at gestation and continues throughout post-fetal life, recapitulating processes in embryonic bone formation (24, 25). Bone morphogenetic proteins act as growth and differentiation factors, and as chemo tactic agents. They stimulate angiogenesis, migration, proliferation, and differentiation of stem cells from the surrounding mesenchymal tissues into bone-forming cells in an area of injury. To be efficacious at a biological target site, BMP-2 must be delivered locally by a suitable carrier system. Numerous materials have been tested for their efficiency in carrying BMP-2. Amongst these materials, collagen, synthetic or natural ceramics, demineralized bone matrix and polyglycolic acid have been most frequently investigated.

However, none of these carrier materials meets all of the requirements of an ideal osteoinductive system (26-28). We have recently investigated

the potential of a dental implant like delivery system for BMP-2 and to facilitate its osteoinductive effects in human, with encouraging clinical results. Moreover, the objective of this study was to evaluate the potential of a purpose designed titanium porous-oxide implant surface combined with rhBMP-2 to stimulate alveolar ridge augmentation.

Materials and methods

Surgical protocol

All the patients included in this study were affected by no space making bone defects according to class III and IV of Cawood and Howell classification. All the defects were horizontal and no vertical bone lost was recorded before the implant placement (29). One hour before surgery the patient received 1 g amoxicillin, and 1 g twice daily for 7 days after the surgical procedure. Surgery was performed under local anaesthesia by the same surgeon. A crestal incision slightly palatal/lingual to the crest in order to preserve a band of keratinized attached mucosa and two vertical release incisions were carried out to reflect a full thickness/muco-periosteal flap.

Ten patients underwent single tooth extraction and immediate implant replacement. In those cases, the dental extraction was performed without mucoperiostal, full thickness flap. The implant site was prepared with standard drills following the palatal bony walls as a guide, and the apical portion of the implant was placed about 3 mm beyond the root apex. To ensure primary stability, the drilling protocol included underpreparation of the implant site without screw tapping or countersinking. The coronal margin of the dental implant was positioned at the palatal level of the bone crest.

Chlorhexidine mouthwash was prescribed to the patients twice daily for the next 15 days.

A total of 20 patients who underwent placement of implants with BMP were reviewed. A total of 38 implants were placed. Eighteen implants were placed in the maxilla and 20 implants in the mandible. Ten post extractive dental implants single tooth were positioned (Figures 1, 2, 3).

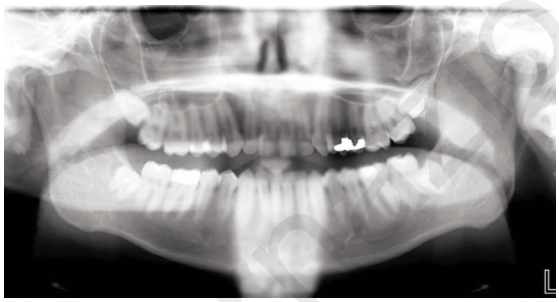

Figure 1
Pre-operative radiographic image.

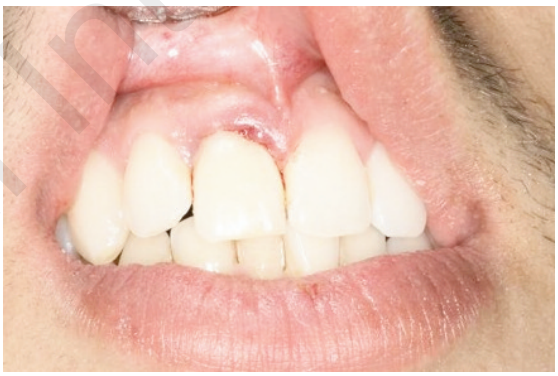

Figure 2
Anterior incisors affected by periodontal disease and undergoing to extraction.

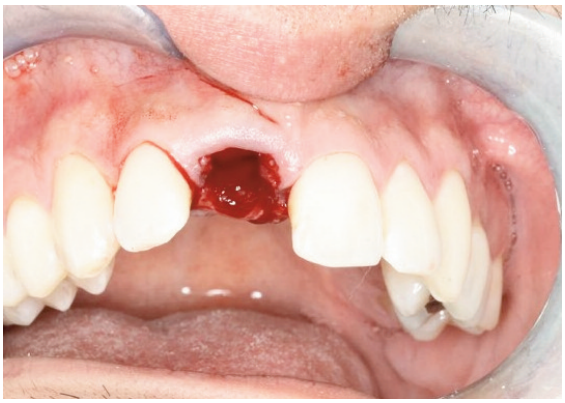

Figure 3
Anterior incisors extraction performed.

Senoj Biocare Inc® provided the dental implants used for this investigation. Implants are made by titanium alloy, medical grade IV (C 0.10 max, Fe 0.20 max, H 0.015 max, N 0.03 max, O 0.18 max, Ti remanent). All implant surface is hydroxyapatite coated and structured with several holes in order to keep the protein *in situ* (Figure 4). The technique involved reconstruction of the alveolar ridge and implant positioning at the same surgery time. The ridges were reconstructed with guided bone regeneration utilizing rhBMP-2. The rhBMP-2 was combined with an allograft (Puros) or xenograft (Bio-Oss) extender and small amount of locally harvested autogenous bone to help maintain the space for bone fill (50% autogenous bone). Implants were placed either at the same time as the bone graft or secondarily, but always at the same surgery (Figures 5, 6). 4 to 8 mg of rhBMP-2 was delivered to the surgical site in concentrations of 1.5 on an absorbable collagen sponge (ACS). The

Figure 4
Dental implant used for the study. The picture shows the holes on the implant surface.

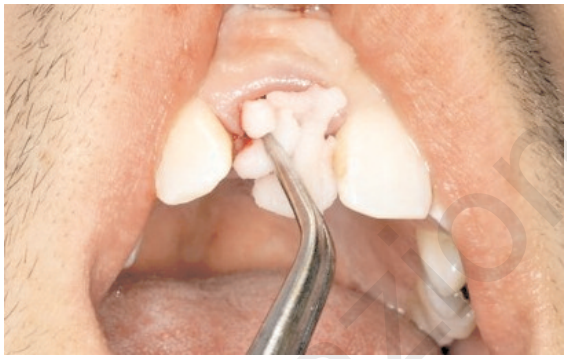

Figure 5
Bmp2 and absorbable collagene sponge placed in the fresh socket after tooth extraction.

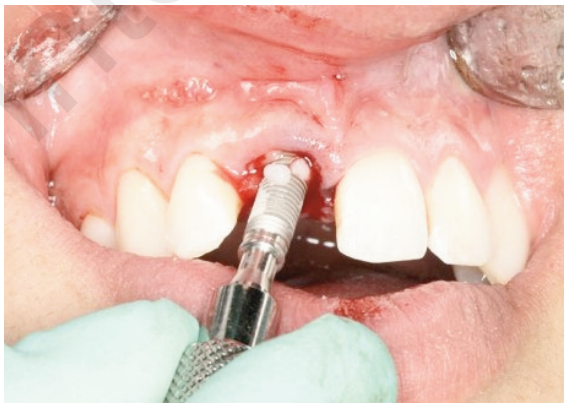

Figure 6
Dental implant placement. A particular shows how positioning of BMP2 and absorbable collagen sponge covers the holes.

rhBMP-2/ACS was then placed into the prepared implant osteotomy as well as the grooves and spaces in the implant itself. No membrane was used to cover the implant. The implants were then allowed to osseointegrate.

Prosthetic protocol

Immediately after the surgical procedure, the patient received a temporary abutment and pros-

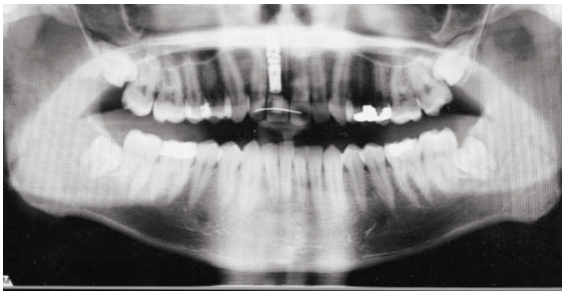

Figure 7
Post op radiographic control after implant placement show that implant is osteointegrated.

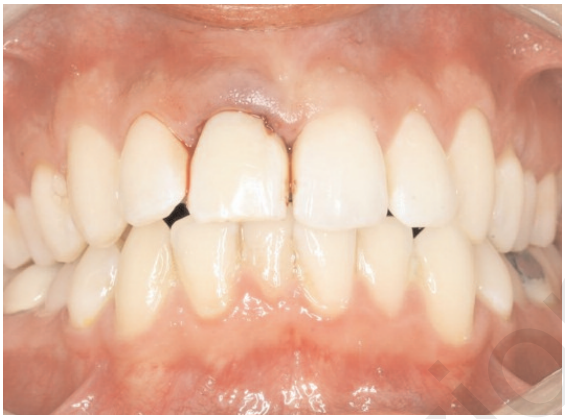

Figure 8
Provisional resin crown is placed over in order to improve soft tissue healing.

thetic restoration. Transfer copings were inserted into the internal hexes of the implant with a seating instrument and secured with abutment screw. An impression was made with a polyether material using an individual impression tray. The temporary crown was cemented even if not maintained in full contact in centric occlusion. The patient followed a soft diet (avoiding bread and meat) for 3 months. After a period of fourteen to seventeen days, 5 of the 10 single implants were then completely restored with ceramic crown and placed into function (Figures 7, 8, 9). Other implants were allowed to heal over a period of six weeks based on bone formation and subsequently restored.

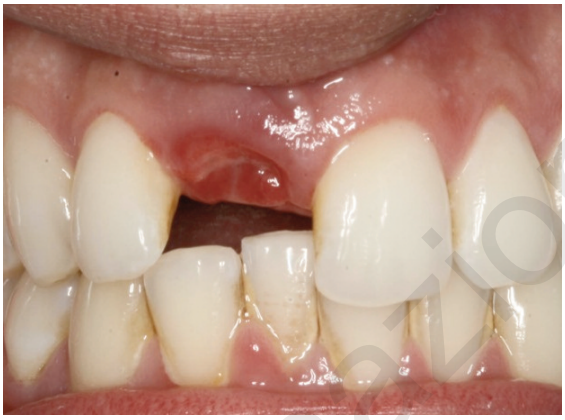

Figure 9
Soft tissue healing after 3 weeks.

Results

Loma Linda University Oral and Maxillofacial Surgery department residents performed follow-up visits every 6 months after implant placement. The following clinical parameters were checked: plaque, bleeding index at four surfaces around the implant, pain, occlusion, and prosthesis mobility. Success criteria for implant survival were implant stability, absence of radiolucency around the implant, mucosal suppuration, and pain. Total follow-up ranged from 12 to 38 months (avg 18.5 mo). Of the 38 implants placed, one implant failed in the mandible. The implant was removed and the area augmented with bone grafted for the posterior mandible area and after 6 months another implant was positioned. Radiographs were used to evaluate osseointegration. Ostel reading was also taken to evaluate stability of the implant (Figures 10, 11, 12). Success was determined based on Albrektsson's criteria (absence of mobility, absence of painful symptoms or paresthesis, absence of peri-implant radiolucency, absence of progressive marginal bone loss) (30). Based on these criteria this patient population had a success rate of 95%.

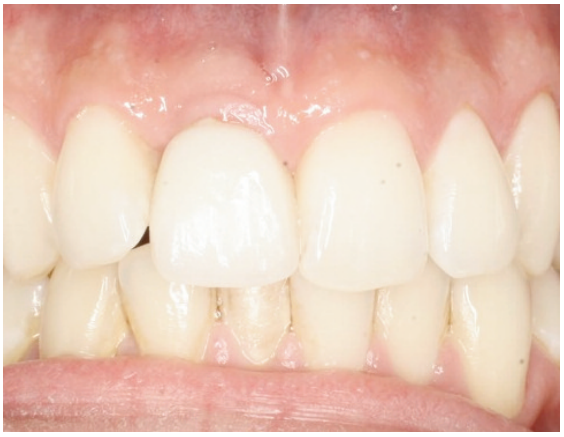

Figure 10
Provisional resin crown cemented of implant abutment at 4 weeks healing time.

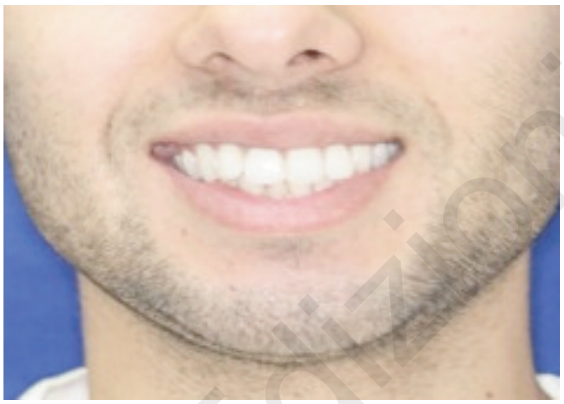

Figure 11
1 year clinical follow up, clinical evaluation.

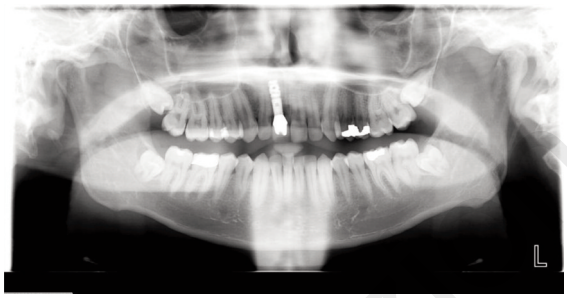

Figure 12
1 year radiographic image.

Discussion

Advantages using autograft bone, the treatment of choice or "gold standard" for skeletal reconstruction, are limited due to limited tissue resources and donor morbidity. Preclinical 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 adjacent resident bone and allows placement, osseointegration, and functional loading of dental implant (30-34). The data results and some recent investigations on dental implants osteointegration clearly underlined how the osteoconductivity of titanium implants can be improved either if their surface properties are modified or if they are coated with a layer of calcium phosphate (35, 36). However, the implants can be rendered osteoinductive only by the introduction of an osteogenic agent, such as bone morphogenetic protein-2 (BMP-2). The BMP-2-carrier potential of numerous materials has been tested at both ectopic and orthotopic sites (37, 38). In all cases, the adsorbed agent was liberated too rapidly to induce a sustained osteogenic response.
Following extensive purification and molecular cloning, recombinant human BMPs (rhBMPs) have been made available for preclinical and clinical evaluation. Indeed, application of rhBMP-2 in craniofacial indications such as alveolar augmentation and sinus lift procedures has confirmed its safety for human use. Potentially, titanium implants coated with a bone inductive factor such as rhBMP-2 may stimulate local bone formation and osseointegration, negating the need for additional bone augmentation with implant procedures (39-42).
The osteoconductivity of metallic implants coating on their surfaces with a layer of either calcium phosphate-based or bone matrix-like material can enhance their application in oral and or-

thopaedic surgery. These inorganic layers are of course three-dimensional lattice works, which can be used to deliver osteoinductive agents to the peri-implant site.

Osteogenic growth factor BMP-2 can be incorporated into calcium phosphate coatings using the biomimetic technique. BMP-2 formed an integral part of the three-dimensional inorganic latticework and was not merely adsorbed upon its surface (42-45).

Furthermore, the osteogenicity of BMP-2 thus incorporated was not only retained but also potentiated in an *in vitro* system comprised of cultured osteoprogenitor cells. Candidate implant surfaces to serve as a vehicle for rhBMP-2 have been evaluated in a rat ectopic model. Titanium disks with turned and titanium porous-oxide surfaces coated with rhBMP-2 were implanted into the ventral thoracic region in rats. The histologic evaluation showed significant bone formation and osseointegration following a 14-day healing interval for titanium porous-oxide surfaces coated with rhBMP-2. A porous-oxide surface with open pores appeared the most effective (45, 46).

A demonstration of the osseoconductive effects of BMP2 within endosseous dental implants was firstly carried out by Boyne in 2004. Through the results of this investigation, Boyne underlined how a dental implant seems to be a bone-induction delivery system if associated with BMP in a non-human animal primate model (47).

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. Osseointegrated implants have been shown to be associated with a high success rate. That success rate however is decreased when significant defects are present which require a grafting procedure. The addition of a growth factor such as rhBMP-2 has the potential to increase the success rates in the challenging areas. Another added benefit would be the likely earlier osseointegration, thus making earlier placement of implants safer. The potential added benefit should be weighed against the additional cost of the procedure (48, 49).

Conclusions

Animal studies have successfully underlined the ability to reconstruct a variety of large and small defects, and now human application involving mandibular continuity defects has been studied. The great potential use for bone growth cytokines rhBMP2 is exciting and offers future and predictable alternatives to traditional grafting techniques. Dental implants can be placed together with rhBMP-2 to provide a successful reconstruction. The titanium porous-oxide implant surface combined with mechanical retention serves as an effective carrier for rhBMP-2 showing a clinically significant potential to stimulate local bone formation, i.e. vertical augmentation of the alveolar ridge. The combination of the dental implant and rhbmp2 seems to guarantee long term stability of the final prosthesis and seems to accelerate the osteointegration process.

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