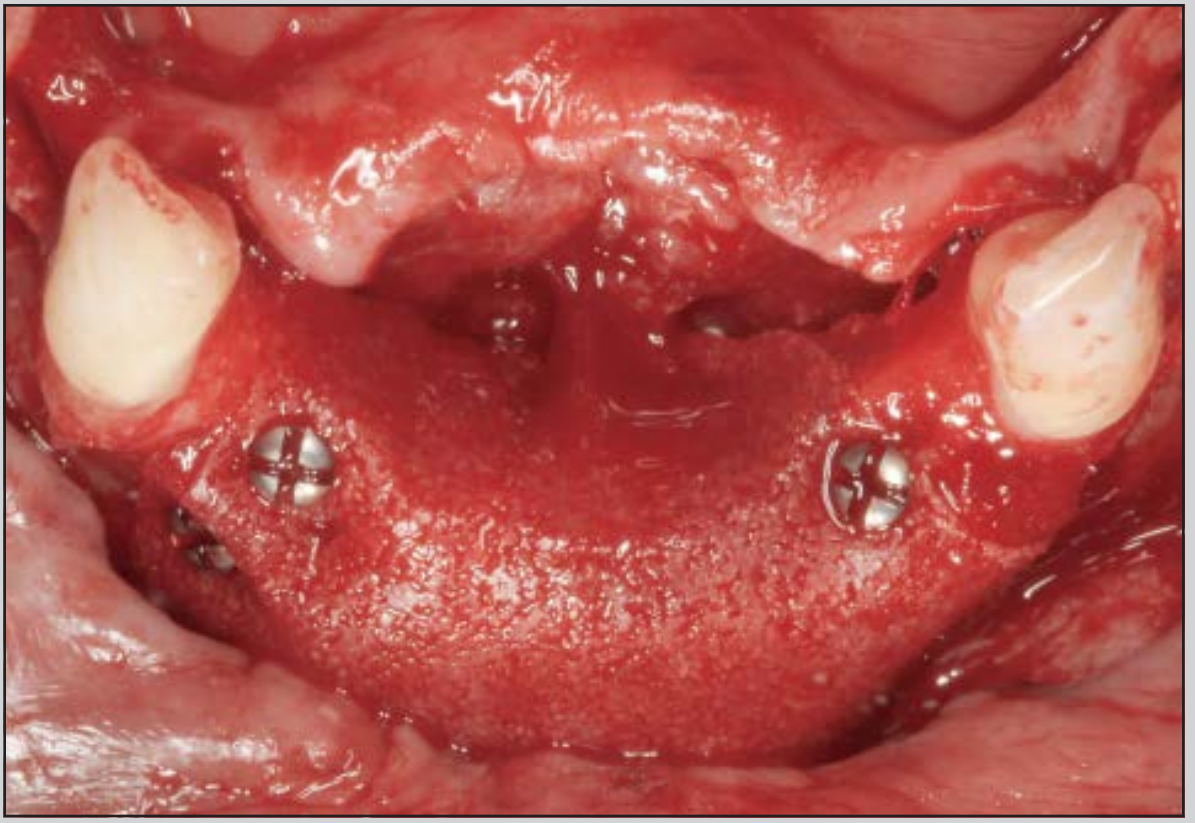
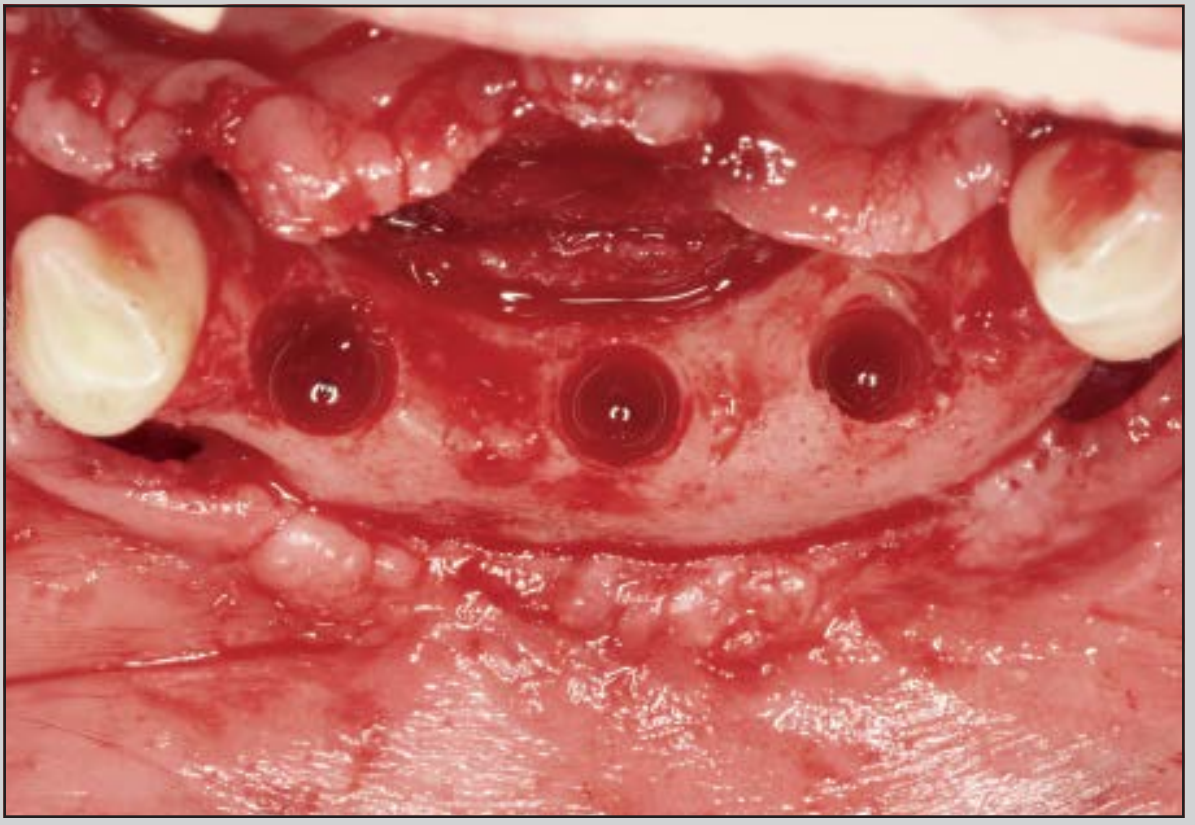




Tissue Engineering for Lateral Ridge Augmentation with Recombinant Human Bone Morphogenetic Protein 2 Combination Therapy: A Case Report

George A. Mandelaris, DDS, MS[1]
Daniel B. Spagnoli, DDS, MS, PhD[2]
Alan L. Rosenfeld, DDS[3]
James McKee, DDS[4]
Mei Lu, DDS, MSD, PhD[5]

This case report describes a tissue-engineered reconstruction with recombinant human bone morphogenetic protein 2/acellular collagen sponge (rhBMP-2/ACS) + cancellous allograft and space maintenance via Medpor Contain mesh in the treatment of a patient requiring maxillary and mandibular horizontal ridge augmentation to enable implant placement. The patient underwent a previously unsuccessful corticocancellous bone graft at these sites. Multiple and contiguous sites in the maxilla and in the mandibular anterior, demonstrating advanced lateral ridge deficiencies, were managed using a tissue engineering approach as an alternative to autogenous bone harvesting. Four maxillary and three mandibular implants were placed 9 and 10 months, respectively, after tissue engineering reconstruction, and all were functioning successfully after 24 months of follow-up. Histomorphometric analysis of a bone core obtained at the time of the maxillary implant placement demonstrated a mean of 76.1% new vital bone formation, 22.2% marrow/cells, and 1.7% residual graft tissue. Tissue engineering for lateral ridge augmentation with combination therapy requires further research to determine predictability and limitations. (Int J Periodontics Restorative Dent 2015;35:325–333. doi: 10.11607/prd.2378)

[1]Private Practice, Park Ridge and Oakbrook Terrace, Illinois; Clinical Assistant Professor, Department of Oral and Maxillofacial Surgery, Louisiana State University, School of Dentistry, New Orleans, Louisiana; Adjunct Clinical Assistant Professor, University of Illinois, School of Dentistry, Department of Graduate Periodontics, Chicago, Illinois, USA.
[2]Associate Professor and Chairman, Department of Oral and Maxillofacial Surgery, Louisiana State University, School of Dentistry, New Orleans, Louisiana, USA.
[3]Clinical Professor, University of Illinois, School of Dentistry, Department of Graduate Periodontics, Chicago, Illinois; Clinical Assistant Professor, Department of Oral and Maxillofacial Surgery, Louisiana State University, School of Dentistry, New Orleans, Louisiana; Private Practice, Park Ridge and Oakbrook Terrace, Illinois, USA.
[4]Private Practice, Downers Grove, Illinois, USA.
[5]Associate Professor, Department of Oral and Maxillofacial Surgery, School of Dentistry, Loma Linda University, Loma Linda, California; Private Practice, Redlands and Chino, California, USA.

Correspondence to: Dr George Mandelaris, 1 S 224 Summit Ave, Suite 205, Oakbrook Terrace, Illinois 60181, USA; fax: 630-627-2148; email: GMandelari@aol.com.

As tissue engineering strategies for replacing missing tissues and organs have emerged, and the osteoinductive properties of bone morphogenetic protein 2 (BMP-2) have been recognized,[1,2] recombinant human BMP 2 (rhBMP-2)/absorbable collagen sponge (ACS; Infuse, Medtronic) has been developed for use in oral and maxillofacial implant sites requiring bone augmentation.[3] Its safety and effectiveness for sinus bone grafting and alveolar bone repair have been investigated in large-scale randomized controlled trials (RCTs).[4–7] rhBMP-2/ACS has demonstrated predictability for inducing de novo bone formation for maxillary sinus and localized alveolar ridge augmentation after tooth extraction procedures.[8–10] This article introduces internal scaffolding via cancellous particulate allograft with external scaffolding by using a mesh that was fixated, thus representing a technique modification to the approved labeling of the Infuse product.

Use of rhBMP-2/ACS for augmenting resorbed alveolar ridges has been subjected to preliminary investigation in both animals and humans.[5,11–16] While results have been variable, successful de novo bone formation has been reported and suggests the need for improved protocols and recommendations, especially when an expanded scope

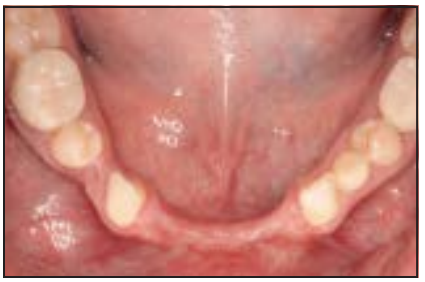


Fig 1 *Mandibular anterior region before treatment.*

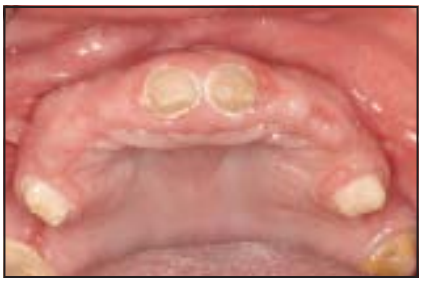


Fig 2 *Preoperative photo of the maxillary arch with the full-arch provisional removed.*

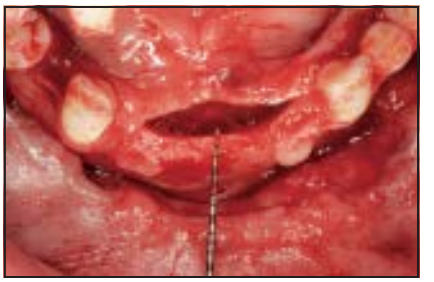


Fig 3 *Flap reflection and regional anatomy of the mandibular anterior. Previous block grafting is observed at both mandibular lateral incisor positions, which was inadequate.*

of bone reconstruction is involved. The use of rhBMP-2/ACS for larger defects or with combination therapies is currently regarded as an off-label application. The purpose of this case report is to present a surgical modification of the on-label tissue engineering approach for lateral ridge augmentation using commercially available rhBMP-2/ACS (Infuse) in the treatment of a patient with several areas of severe localized ridge deficiencies in the maxillary and mandibular arches. Based on developmental principles of intramembranous bone growth in the patient's skeleton, it is important to provide space maintenance in any site where one chooses to increase the dimension of the bone. Clinical reentry documentation, pre- and postoperative cone beam computed tomography (CBCT) scans, and histomorphometric analysis of a bone core are presented, which demonstrated a high percentage of vital bone formation along with sufficient de novo bone formation volume to enable optimal, prosthetically directed implant placement.

Case report

A 24-year-old Caucasian male (nonsmoker) presented in good general health and with a dental history that included congenital anodontia as well as the loss of multiple teeth due to dental caries. Severe maxillary alveolar defects were present bilaterally, along with extensive (and primarily) horizontal atrophy of the anterior mandible. Previous maxillary and mandibular ridge augmentation using intraorally harvested corticocancellous block and particulate autogenous bone from the anterior mandible had been provided (without use of a barrier membrane or mesh) but was ineffective in establishing adequate bone width for implant placement. Most of the residual dimensions were either inadequate or, at several sites, had additional bone loss after the primary grafting surgery, as revealed by CBCT imaging. In the mandibular anterior where the block grafting was harvested, the bone dimensions were even more severely deficient compared to initial CBCT scan results. The cross-sectional imaging regional anatomy at the initial examination, 6 months after primary bone grafting, and at 8 to 9 months after tissue engineering validated the need for further augmentation to enable implant placement (see Figs 10 to 12).

After patient diagnosis, based on clinical examination (Figs 1 and 2) and postprimary augmentation imaging findings, the patient was presented with three options: conventional fixed prosthodontics, extraoral bone harvesting for guided bone regeneration, or off-label tissue engineering via rhBMP-2/ACS + cancellous allograft with mesh. Risks and benefits were discussed for informed consent and disclosure. A surgical modification of the on-label approved use of rhBMP-2/ACS (Infuse) was chosen by the patient.

Augmentation of the mandibular anterior and maxillary first premolar to lateral incisor sites was carried out in two separate procedures (2 months apart), using similar surgical techniques. One hour before surgery, 2.0 g amoxicillin was ad-

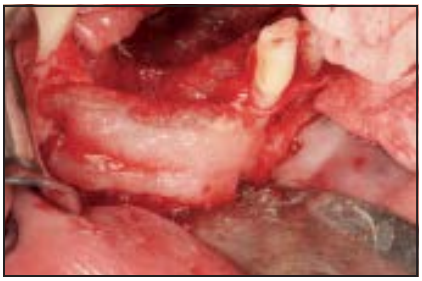


Fig 4 *The rhBMP-2/ACS + cancellous allograft impregnated sponges in place.*

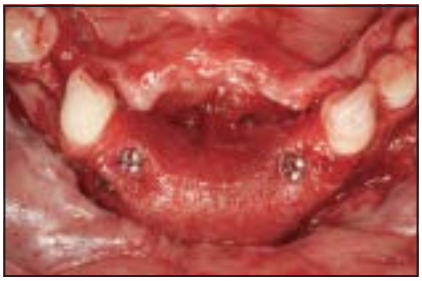


Fig 5 *Medpor Contain fixated by neuroscrews.*

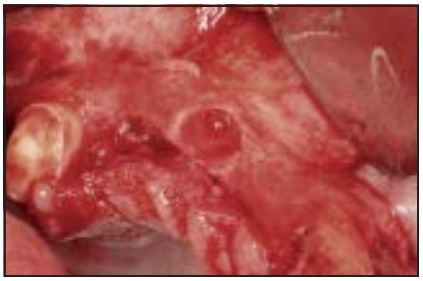


Fig 6 *Maxillary right regional anatomy. Deficient bone grafting and poor socket healing are noted.*

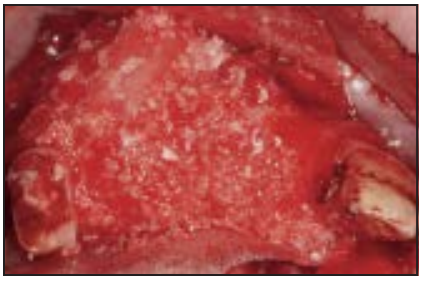


Fig 7 *Maxillary right reconstruction via rhBMP-2/ACS + cancellous allograft with Medpor Contain fixated at the apical base for stabilization.*

Fig 8 *Flap reflection of the left maxilla. Poor socket bone healing is noted as well as severe lateral ridge deficiencies.*

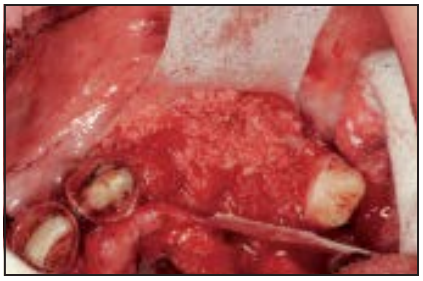


Fig 9 *Maxillary left reconstruction via rhBMP-2/ACS + cancellous allograft in place with Medpor Contain fixated at the apical base.*

ministered. In the mandible, 1.4 mL of rhBMP-2/ACS x-small kit, Infuse) was mixed with 1 mL of freeze-dried cancellous particulate allograft (0.25- to 1-mm particle size) (Cancellous Puros, Zimmer Dental). In the maxillary reconstruction, a total of 3.5 mL of rhBMP-2/ACS (one small Infuse Kit and one xx-small Infuse Kit) was combined with 1 mL of the particulate allograft and used equally on each side of the jaw. For both procedures, the ACS provided in the kits was used as the carrier of the rhBMP-2 molecule.

The surgical field was first prepared by proper flap design, allowing for the ridge relationship to be visualized and to enable proper palatal/lingual as well as facial application of the rhBMP-2/ACS + cancellous allograft construct. During flap development, the scrub team processed the rhBMP-2 protein component per the manufacturer's directions. After its reconstitution, the rhBMP-2 was evenly expressed onto the ACS and allowed to bind for at least 15 minutes. It was then cut into small sections, and all sides were coated with the cancellous allograft.

Following broad, full-thickness dissection and regional anatomy identification, stabilization of the porous polyethylene matrix (Medpor Contain, Stryker) was performed by rigid fixation (multiple 1.5 × 5 mm Neuro Screws, Stryker). Cortical perforations were made in the mandible to encourage angiogenesis. The rhBMP-2/ACS + cancellous allograft was then layered into the space, filling all voids and developing the required dimensions desired for prosthetically directed bone augmentation. The plan was to produce a ridge width of at least 6 mm, which would allow for 4.1-mm-diameter implants to be placed. Further, the authors ensured that all of the collagen sponge became infiltrated with blood (see Figs 4, 7, and 9). In the maxilla, two Medpor Contain matrices were used per side. One was fixated on the buccal to basal bone and one on the palatal basal bone (see Figs 7 and 9). They were then folded to enable containment of the tissue-engineered reconstruction and sutured together, thereby stabilizing the new ridge anatomy. In the mandible, one Medpor

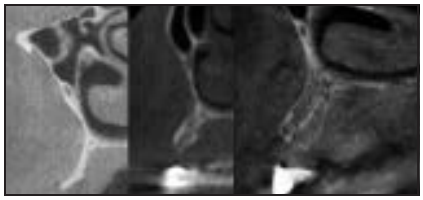


Fig 10 *Cone beam computed tomography (CBCT) cross-sectional imaging of maxillary right first premolar site at* (left) *initial examination,* (center) *6 months after corticocancellous bone grafting, and* (right) *6 months post–tissue engineering via rhBMP-2/ACS + cancellous allograft.*

Fig 11 *CBCT cross-sectional imaging of the maxillary left first premolar site at* (left) *initial examination,* (center) *6 months after corticocancellous bone grafting, and* (right) *6 months post–tissue engineering via rhBMP-2/ACS + cancellous allograft.*

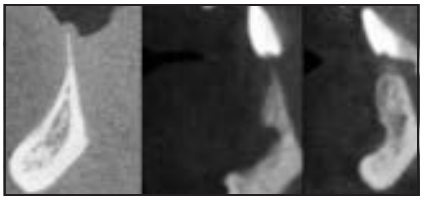
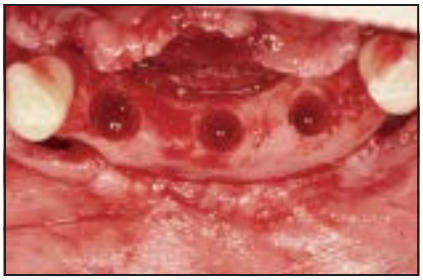
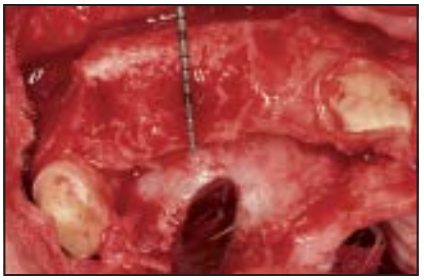
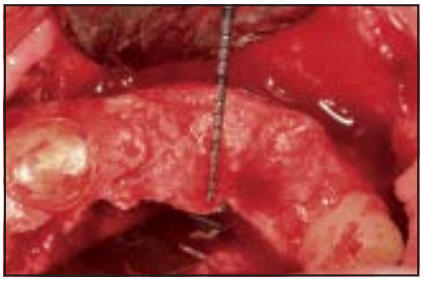


Fig 12 *CBCT cross-sectional imaging of the mandibular left lateral incisor site at* (left) *initial examination,* (center) *6 months after corticocancellous bone grafting, and* (right) *8 months postt–issue engineering via rhBMP-2/ACS + cancellous allograft.*







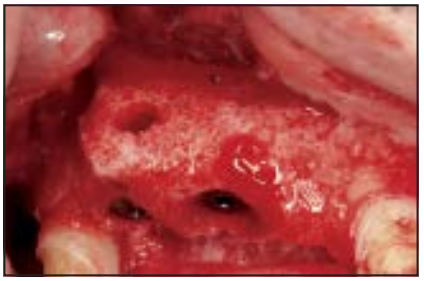


Fig 13 (left) *rhBMP-2/ACS + cancellous allograft reconstructive surgery results at 10 months in the mandibular anterior. Osteotomy site preparation required tapping due to high bone density.*

Fig 14 (right) *Clinical reentry results of the tissue-engineered maxillary right first premolar to lateral incisor sites 9 months after rhBMP-2/ACS + cancellous allograft for lateral ridge augmentation of contiguous defects.*

Fig 15 (left) *Clinical reentry of the maxillary left tissue-engineered section 9 months after rhBMP-2/ACS + cancellous allograft–mediated lateral ridge augmentation for tissue engineering of contiguous defects.*

Fig 16 (right) *Bone core biopsy specimen secured of de novo bone formation and subcrestal implant placement performed at the first premolar and canine positions.*

Contain mesh was fixated at four points (two crestal and two buccal), using the same type of bone fixation screws used in the maxillary reconstruction (Fig 5). Thereafter, flaps were prepared for passive closure using releasing incisions to ensure tension-free closure. Figures 3 to 9 demonstrate the reconstructive tissue engineering surgeries. A tooth-supported provisional was adapted in the maxilla and re-cemented following closure to ensure that lack of pressure would occur to the reconstruction site. The patient did not utilize any form of provisional tooth replacement in the mandibular arch during healing. Postoperative antibiotics (amoxicillin 500 mg every 8 hours for 10 days) and analgesics (600 mg Motrin every 6 hours, as needed) were given, and the patient was started on 0.12% chlorhexidine gluconate after the first follow-up visit. Healing of the grafted sites was uneventful and primary closure was maintained throughout the healing period.

Eight months after mandibular surgery and 6 months after the maxillary procedure, a postoperative CBCT scan was obtained. Imaging data indicated that the ridge width had increased to the prescribed dimensions at all sites (Figs 10 to 12). The Digital Imaging Communication In Medicine (DICOM) data were then converted to a Simplant (Dentsply) file for use in executing CT-guided implant placement using the Tapered Navigator system (Biomet 3i).[17]

Mandibular reentry surgery for implant placement was done after 10 months of healing. Full-thickness

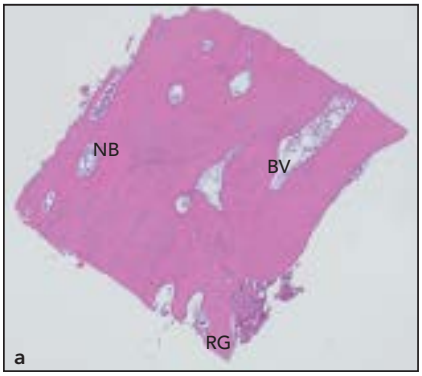


Fig 17a *Histology of bone core biopsy specimen at original magnification ×4, hematoxylin-eosin (h&e) stain, demonstrating a mean of 76.1% new vital bone formation* (NB)*, 22.2% marrow/cells* (BV)*, and 1.7% residual graft tissue* (RG).

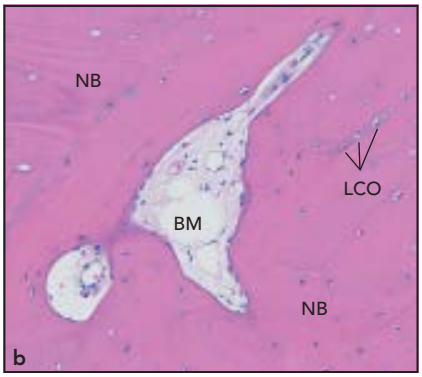


Fig 17b *Histology of bone core biopsy specimen at higher magnification (original magnification ×40, h&e) showing the detailed new bone* (NB)*, bone marrow and cells* (BM)*, and the lacunae-containing osteocytes* (LCO) *surrounded by bone matrix.*

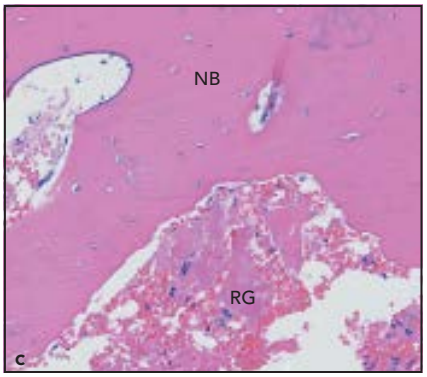


Fig 17c *Histology of bone core biopsy specimen at higher magnification (original magnification ×40, h&e) showing the detailed new bone* (NB) *and residual graft material* (RG).

flap reflection allowed for removal of the bone fixation screws and Medpor Contain mesh via sharp dissection. Implant osteotomies were created in the right lateral incisor and left central and lateral incisor positions (Fig 13). There were no observable residual allograft remnants, and the bone quality required tapping of all three sites prior to implant placement. High primary stability was achieved for each of the three implants placed (4.1-mm-diameter NanoTite Certain, Biomet 3i). Encode healing abutments (Biomet 3i) were immediately connected to the implants.

The right and left maxillary implants were placed 3.5 weeks following mandibular implant placement (roughly 9 months post–tissue engineered reconstruction). Full-thickness flaps were reflected, and the Medpor Contain was removed, except at the basal component where bone fixation screws were not removed (Figs 14 and 15). Bone fixation screws were retained because extensive flap reflection would be required for their removal, resulting in detrimental exposure of the newly regenerated de novo bone. The fixation screws were considered a low therapeutic risk to implant placement and postoperative complications. Before preparation of the osteotomies, a 4-mm-long buccopalatally oriented bone core was obtained from the right first premolar area using a 2-mm-diameter trephine bur (Salvin Dental; Fig 16). Using a stereolithographic tooth-mucosal–supported Tapered Navigator Surgiguide, implants were placed subcrestally in the maxillary first molar, first premolar, and canine positions on each side, cover screws placed, and the tissue was approximated in a tension-free manner for primary closure.

The maxillary bone core specimen was stored in 4% paraformaldehyde and subsequently prepared for histologic and histomorphometric analysis. It was placed in 70% ethanol and sequentially dehydrated in 95% and 100% ethanol. The sample was embedded for 4 to 5 hours in an aqueous encapsulating gel, placed into a mega-cassette, and embedded in celloidin-paraffin. Using a microtome, 5-µm sections were obtained and stained with hematoxylin-eosin (h&e). Whole-slide microphotographs were captured using a whole-slide scanning microscope (Olympus VS120). Histomorphometry was performed under original magnification ×4 using Image-Pro quantitative analysis software at the Philip Boyne Bone laboratory of Loma Linda University, School of Dentistry, Loma Linda, California.

Results

Five slides were selected for histomorphometry. The mean of these five slides was 76.1% new vital bone formation, 22.2% marrow/cells, and 1.7% residual graft tissue. Figures 17a to 17c demonstrate the

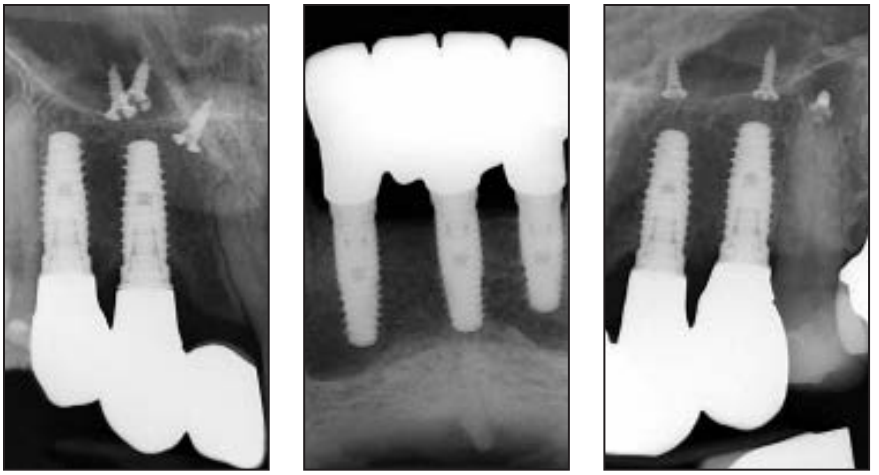


Fig 18 *Radiographs at 24 months postloading of the maxillary left and right first premolar and canine sites and the mandibular anterior tissue-engineered sites supporting osseointegrated dental implants. Bone fixation screws were retained.*

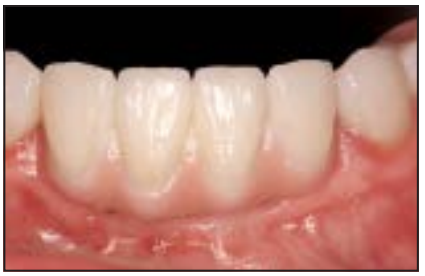
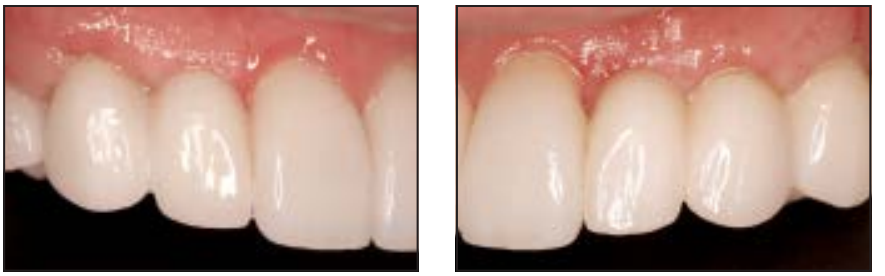


Fig 19 *Clinical outcome of mandibular anterior reconstruction at 24 months postloading.*



Figs 20 and 21 *Clinical outcome of the maxillary right and left reconstruction at 24 months postloading.*

histology obtained from the de novo bone core taken at the implant placement surgery.

In both arches and at all sites, the implants healed unremarkably. Five-and-a-half months following maxillary implant placement, stage-two surgery/uncovery was performed and Encode healing abutments placed. In addition, an interpositional soft tissue graft (Perioderm, Dentsply) was performed from the maxillary right and left first molar to lateral incisor sites to augment soft tissue dimensions at the implant, pontic, and natural first premolar positions. After 24 months of follow-up and prosthetic loading, the definitive restorations were functioning well and with excellent clinical and radiographic peri-implant outcome success (Figs 18 to 21).

Discussion

A paradigm shift occurs when laboratory-based research becomes applied to patient care. Tissue engineering via the use of signaling molecules and morphogens, such as rhBMP-2/ACS, represents such a shift and is becoming increasingly popular. The movement from osteoconductive to osteoinductive regenerative materials and the use of space-maintenance devices are an opportunity to solve many anatomical challenges with greater predictability and less invasiveness. Although a number of reports have demonstrated successful results when using rhBMP-2/ACS in conjunction with sinus elevation and extraction socket procedures,[8–10,14,15] when rhBMP-2/ACS has been used for lateral ridge augmentation, the results have been somewhat inconsistent, apparently attributed to the limited scaffold/matrix systems utilized in these early reports. Limited to no new bone formation was found in one feasibility study, with the poor results attributed to collapse of the collagen sponge.[4] Conversely, favorable results have

been reported when tenting screws were used for space maintenance.[11] A 2013 RCT that compared the use of rhBMP-2/ACS with autogenous bone for augmentation of atrophic anterior maxillary sites found that rhBMP-2/ACS yielded significantly greater radiographic horizontal bone gain compared with autogenous bone at immediate subcrestal levels (1.5 ± 0.7 versus 0.5 ± 0.9 mm; $P = .01$). No significant differences were found at midcrestal or apical levels or in clinical horizontal bone gain, suggesting that rhBMP-2/ACS is a realistic alternative to autogenous bone.[18]

The patient in this case report originally had corticocancellous onlay grafting harvested from the mandibular symphysis, which did not provide sufficient bone volume and, in fact, resulted in a more significant deficit in the mandibular anterior region. Based on the CBCT imaging pre–tissue engineering reconstruction, it was determined that the patient did not have sufficient intraoral autogenous bone to donate for secondary site development surgery. His options for an implant–tooth-replacement solution, therefore, included extraoral bone harvesting for guided bone regeneration efforts or an off-label tissue engineering approach using rhBMP-2/ACS (which he ultimately chose to proceed with).

The rhBMP-2/ACS product is approved for sinus elevation and localized alveolar ridge augmentation associated with extraction sockets.[19] It currently is not approved for multiple and contiguous sites for alveolar ridge augmentation nor is it approved for use in combination with allograft. In the case presented here, off-label utilization of rhBMP-2/ACS was performed with informed consent from the patient in an attempt to satisfy bone augmentation requirements and to avoid additional donor site morbidity. The authors used a surgical modification of the on-label tissue engineering approach by incorporating cancellous particulate allograft as an internal scaffold for the purpose of increasing the surface area available for adherence by newly recruited mesenchymal stem cells. The histologic results yielded an impressive percentage of vital bone formation to support osseointegration. However, the histology from this case report cannot be considered definitive because the core sample was small, was of limited depth, was a single specimen, and was taken in the buccopalatal direction only.

Medpor Contain is a high-density porous polyethylene alloplast and was chosen to provide space maintenance based on its known properties, including tissue biocompatibility, vascular ingrowth, favorable tissue integration, high tensile strength, and resistance to fatigue as well as its ability to be fixated.[20,21] Its architecture served as an external scaffold in that it does not block neovascularization or vascular ingrowth during healing. It also does not interfere with radiographic evaluation.

Clinical reentry demonstrated adequate bone volume to enable prosthetically directed implant placement. The morphology and contours of the rhBMP-2/ACS + cancellous allograft–generated sites were similar to native bone, with distinct vascularization even at the coronal and/or lateral most aspects of the ridge's reconstructions. It was difficult (if not impossible) to visually distinguish between native bone and the de novo regenerated bone. The quality of the bone required tapping of the mandibular implant sites, and primary stability was obtained for all implants placed. Pre–tissue engineering ridge width measurements in the anterior mandible ranged from to 1.1 to 3.4 mm (mean = 2.25 mm) as measured by CBCT cross sectionals. At 8 months, the post–tissue engineering reconstruction CBCT imaging showed that these areas measured 6.5 to 7.0 mm (mean = 6.75 mm). The mean horizontal ridge width gain in the mandible was 4.5 mm. Pre–tissue engineering ridge width measurements in the maxillary right and left regions ranged from 1.9 to 3.4 mm (mean = 2.65 mm) as determined by CBCT imaging. The 6-month post–tissue engineering CBCT scan showed horizontal ridge width dimensions ranging from 7.4 to 9.3 mm (mean = 8.35 mm). The mean horizontal ridge width gain in the maxilla was 5.7 mm.

Posttreatment CBCT imaging demonstrated greater bone density in the mandibular reconstruction. The authors elected to pursue CT-guided implant placement in the maxillary arch first because a longer osseointegration period was anticipated compared to the mandibular anterior site. This post–tissue engineering decision was based on mineral density observations

of cross-sectional and axial CBCT slices.[22,23] A submerged approach was implemented in the maxilla and a 5-month osseointegration period allowed prior to uncovery and healing abutment placement. A full-arch, tooth-supported metal-ceramic provisional was used during surgical treatment and until implant osseointegration was confirmed, at which time the patient was transitioned to screw-retained implant-supported provisionals. In the mandible, high bone density was noted and required tapping of the osteotomy sites. This was consistent with the bone density observed on post–tissue engineering CBCT imaging. A one-stage surgery was performed and a 2- to 3-month osseointegration was observed prior to occlusal loading with a screw-retained provisional. Provisionals were used for 3 months to groom soft tissues and ensure a favorable response to occlusal loading and phonetics. Maxillary lateral incisor implants were avoided due to the distal root inclinations of the maxillary central incisors. The maxillary first premolar and canine positions were chosen bilaterally along with cantilevered lateral incisors because these sites allowed for the most favorable implant diameters and optimal positioning as directed by the diagnostic wax-up and prosthetic outcome goals.

The percentage of residual graft in this case report was minimal (1.7%) and less than that reported in the literature where rhBMP-2/ACS was not used.[24–26] There was increased resorption and replacement of the cancellous allograft, which coincided with a favorable percentage of new vital bone formation, further supporting the use of cancellous bone and its rapid vascularization.[27] Comparatively, Feuille et al reported a mean of 52.4% residual graft particles when particulate, mineralized, cortical freeze-dried bone allograft alone was used in combination with a titanium-reinforced expanded polytetrafluoroethylene barrier in the treatment of localized alveolar ridge deficiencies.[28] Future studies are needed to determine whether the addition of rhBMP-2/ACS upregulates osteoclastic activity when used in combination with an allograft minimizing residual graft particles and which, if any, bone substitute material + rhBMP-2/ACS combination optimizes de novo bone formation outcomes compared to rhBMP/ACS + space maintenance alone.

The use of rhBMP-2/ACS may induce bone formation and enhance cancellous graft replacement throughout the reconstruction more favorably compared to an osteoconductive mediated guided bone regeneration approach where more passive biomaterials such as allografts or xenografts are predominantly used. In such approaches, observing unincorporated bone substitute particles is not uncommon clinically, and those particles generally present on the outer periphery of the graft augmentation or at the center of the socket. This underscores the distinct difference of a tissue-engineered, osteoinductive approach for site development using rhBMP-2/ACS, which recapitulates embryonic intramembranous bone growth compared to one that relies on a creeping substitution healing pattern. The combination of primary wound closure, angiogenesis (further enhanced by the osteoinductive molecule rhBMP-2), space maintenance, and wound stability (ie, PASS principle) cannot be overemphasized in any reconstructive surgery effort.[29] In addition, the inherent wound healing capability and compliance of the patient also account for the excellent results obtained in this complex reconstruction outcome.

Conclusions

Emerging osteoinductive materials show great promise in expanding and improving the opportunities for bone regeneration with less invasiveness and high predictability. The results of this off-label case report demonstrate favorable de novo bone formation and a high percentage of vital bone formation by use of a potent osteoinductive agent, rhBMP-2, in conjunction with cancellous allograft to support successful osseointegration. RCTs are required to determine appropriate protocols for such expanded applications of currently regarded off-label rhBMP-2/ACS approaches.

Acknowledgments

The authors reported no conflicts of interest related to this study.

References

1. Urist MR. Bone: Formation by autoinduction. Science 1965;150:893–899.
2. Lind M. Growth factors stimulation of bone healing. Effects on osteoblast, osteotomies, and implant fixation. Acta Orthop Scand Suppl 1998;283:2–37.
3. Spagnoli DB, Marx RE. Dental implants and the use of rhBMP-2. Dent Clin North Am 2011;55:883–907.
4. Howell TH, Fiorellini J, Jones A, et al. A feasibility study evaluating rhBMP-2/absorbable collagen sponge device for local alveolar ridge preservation or augmentation. Int J Periodontics Restorative Dent 1997;17:124–139.
5. Cochran DL, Jones AA, Lilly LC, Fiorellini JP, Howell H. Evaluation of recombinant human bone morphogenetic protein-2 in oral applications including the use of endosseous implants: 3-year results of a pilot study in humans. J Periodontol 2000;71:1241–1257.
6. Fiorellini JP, Howell TH, Cochran D, et al. Randomized study evaluating recombinant human bone morphogenetic protein-2 for extraction socket augmentation. J Periodontol 2005;76:605–613.
7. Thawani JP, Wang AC, Than KD, et al. Bone morphogenetic proteins and cancer: Review of the literature. Neurosurgery 2010;66:233–246.
8. Boyne PJ, Lilly LC, Marx RE, et al. De novo bone induction by recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillary sinus floor augmentation. J Oral Maxillofac Surg 2005;63:1693–1707.
9. Triplett RG, Nevins M, Marx RE, et al. Pivotal, randomized, parallel evaluation of recombinant human bone morphogenetic protein-2/absorbable collagen sponge and autogenous bone graft for maxillary sinus floor augmentation. J Oral Maxillofac Surg 2009;67:1947–1960.
10. Misch CM. The use of recombinant human bone morphogenetic protein-2 for the repair of extraction socket defects: A technical modification and case series report. Int J Oral Maxillofac Implants 2010;25:1246–1252.
11. Mehanna R, Koo S, Kim DM. Recombinant human bone morphogenetic protein 2 in lateral ridge augmentation. Int J Periodontics Restorative Dent 2013;33:97–102.
12. de Freitas RM, Susin C, Spin-Neto R, et al. Horizontal ridge augmentation of the atrophic anterior maxilla using rhBMP-2/ACS or autogenous bone grafts: A proof-of-concept randomized clinical trial. J Clin Periodontol 2013;40:968–975.
13. Jung RE, Thoma DS, Hämmerle CH. Assessment of the potential of growth factors for localized alveolar ridge augmentation: A systematic review. J Clin Periodontol 2008;35(suppl 8):255–281.
14. Jung RE, Glauser R, Schärer P, Hämmerle CH, Sailer HF, Weber FE. Effect of rhBMP-2 on guided bone regeneration in humans. Clin Oral Implants Res 2003;14:556–568.
15. Thoma DS, Jones A, Yamashita M, Edmunds R, Nevins M, Cochran DL. Ridge augmentation using recombinant bone morphogenetic protein-2 techniques: An experimental study in the canine. J Periodontol 2010;81:1829–1838.
16. Yamashita M, Nevins M, Jones AA, Schoolfield J, Cochran DL. A pilot experimental lateral ridge augmentation study using bone morphogenetic protein 2 in dogs. Int J Periodontics Restorative Dent 2010;30:457–469.
17. Testori T, Robiony M, Parenti A, et al. Evaluation of accuracy and precision of a new guided surgery system: A multicenter clinical study. Int J Periodontics Restorative Dent 2014;34(suppl):s59–s69.
18. Coomes AM, Mealey BL, Huynh-Ba G, et al. Buccal bone formation after flapless extraction: A randomized, controlled clinical trial comparing recombinant human bone morphogenetic protein 2/absorbable collagen carrier and collagen sponge alone. J Periodontol 2014;85:525–535.
19. Carter TG, Brar PS, Tolas A, Beirne OR. Off-label use of recombinant human bone morphogenetic protein-2 (rhBMP-2) for reconstruction of mandibular bone defects in humans. J Oral Maxillofac Surg 2008;66:1417–1425.
20. Frodel JL, Lee S. The use of high-density porous polyethylene implants in facial deformities. Arch Otolaryngol Head Neck Surg 1998;124:1219–1223.
21. Romano JJ, Iliff NT, Manson PN. Use of Medpor porous polythelene implants in 140 patients with facial fractures. J Craniofac Surg 1993;4:142–147.
22. González-Garcia R, Monje F. The reliability of cone-beam computed tomography to assess bone density at dental implant recipient sites: A histomorphometric analysis by mirco-CT. Clin Oral Implants Res 2013;24:871–879.
23. Isoda K, Ayukawa Y, Tsukiyama Y, Sogo M, Matsushita Y, Koyano K. Relationship between the bone density estimated by cone-beam computed tomography and the primary stability of dental implants. Clin Oral Implants Res 2012;23:832–836.
24. Schmitt CM, Doering H, Schmidt T, Lutz R, Neukam FW, Schlegel KA. Histological results after maxillary sinus augmentation with Straumann Bone Ceramic, Bio-Oss, Puros and autogenous bone. A randomized clinical trial. Clin Oral Implants Res 2013;24:576–585.
25. Noumbussi SS, Lozada JL, Rohrer MD, Clem D, Kim JS, Prasad H. Clinical, histological, and histomorphometric evaluation of mineralized solvent-dehydrated bone allograft (Puros) in human maxillary sinus grafts. J Oral Implantol 2005;31:171–179.
26. Froum SJ, Wallace SW, Elian NE, Cho SC, Tarnow DP. Comparison of mineralized freeze cancellous bone allograft (Puros) and anorganic bovine bone matrix (Bio-Oss) for sinus augmentation: Histomorphometry at 26 to 32 weeks after grafting. Int J Periodotics Restorative Dent 2006;26:543–551.
27. Burchardt H. The biology of bone graft repair. Clin Orthop Relat Res 1983;(174):28–42.
28. Feuille F, Knapp CL, Brunsvold MA, Mellonig JT. Clinical and histologic evaluation of bone-replacement grafts in the treatment of localized alveolar ridge defects. Part I: Mineralized freeze-dried bone allograft. Int J Periodontics Restorative Dent 2003;23:29–35.
29. Wang HL, Boyapati L. PASS principles for predictable bone regeneration. Implant Dent 2006;15:8–17.