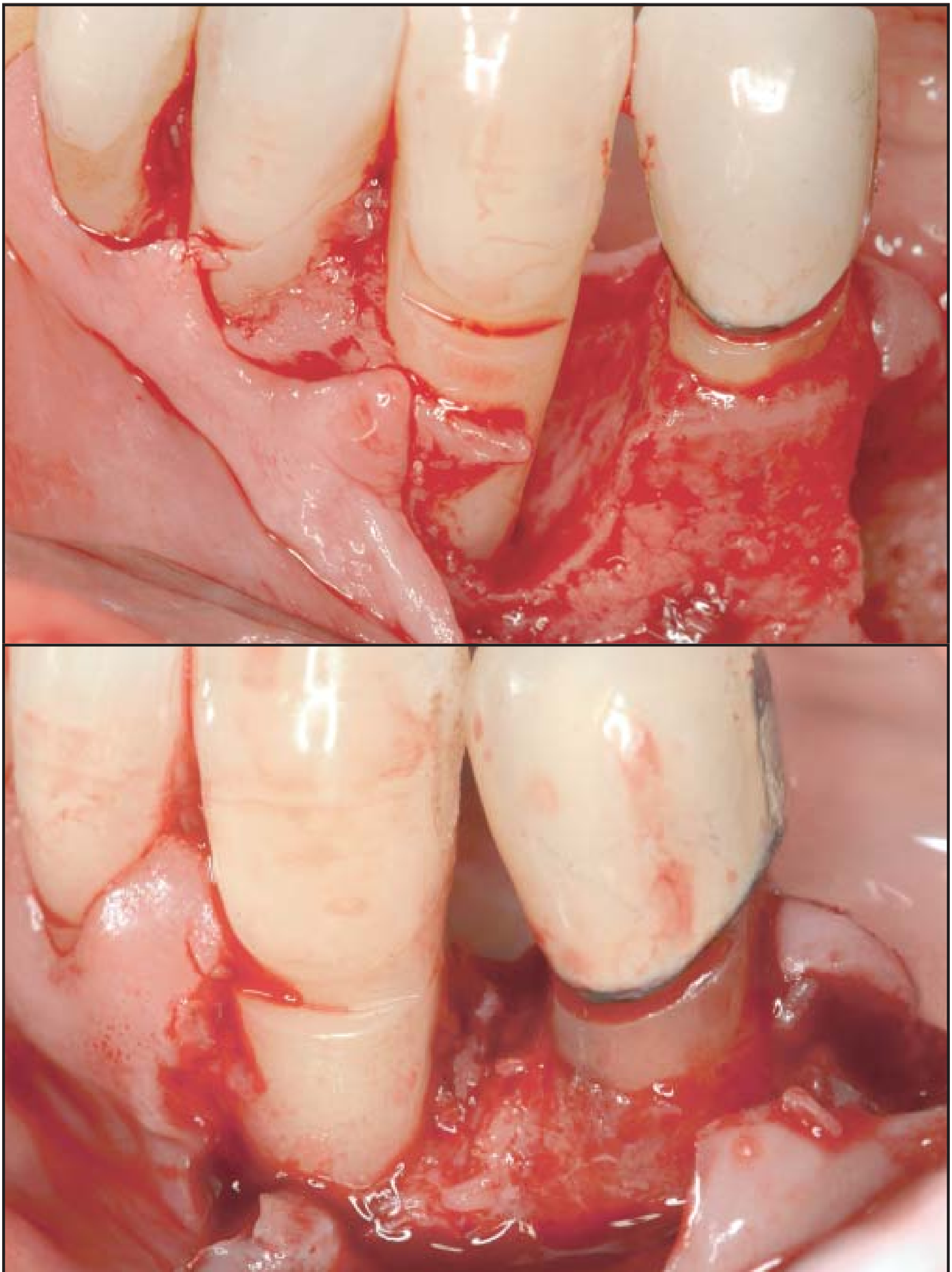

A Retrospective Consecutive Case Series Using Mineralized Allograft Combined with Recombinant Human Platelet-Derived Growth Factor BB to Treat Moderate to Severe Osseous Lesions

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This retrospective case series reports on the use of freeze-dried bone allograft (FDBA) combined with a purified recombinant protein of platelet-derived growth factor BB (PDGF-BB) for the treatment of periodontal intraosseous defects in 50 consecutive patients. The mean pretreatment measurements for clinical attachment level and probing depth were 7.9 ± 1.6 mm and 7.8 ± 1.4 mm, respectively. At 6 months, mean clinical attachment level was 3.9 ± 1.4 mm, reflecting an improvement of 4.1 ± 1.3 mm, whereas mean probing depth was reduced to 3.0 ± 1.2 mm, corresponding to a reduction of 4.8 ± 1.4 mm. These clinical results indicate that the combined use of FDBA and PDGF-BB can lead to substantial improvements in clinical parameters. (Int J Periodontics Restorative Dent 2011;31:335–342.)

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The development of growth factors for regenerative therapy has enhanced the capability of clinicians to maintain teeth with advanced intraosseous lesions.[1–3] The earliest efforts with regenerative therapy focused on a variety of autogenous bone sources to achieve restitution of the attachment apparatus, including new bone, cementum, and a functional periodontal ligament to a root surface previously exposed to the oral environment.[4–9] While results may have demonstrated some variation, the greatest issue was the morbidity in harvesting the graft and the finite supply of bone.[9,10]

Subsequent efforts have focused on the use of banked human bone,[11] alloplasts,[12–17] and xenografts[18–20] as substitutes for the gold standard of autogenous bone and marrow from the iliac crest. While the use of alternative graft materials has reduced the concern of morbidity, the inconsistency in clinical and histologic outcomes has left clinicians uncertain about the most effective material. Clinicians have typically selected demineralized freeze-dried bone allograft (DFDBA), which has demonstrated osteoinductive capacity,[21–23] or bovine-derived anorganic bone matrix.[24] However, studies suggest that differences in procurement and processing of DFDBA[25,26] can result in variation in overall clinical and biologic activity, including the effectiveness of the graft in maintaining space. Moreover, bovine-derived anorganic bone appears to have limited capacity to support periodontal regeneration in humans, unless used in combination with a barrier membrane.[20]

Most recently, a highly purified protein, recombinant platelet-derived growth factor BB (PDGF-BB), has been developed and marketed with a synthetic matrix of β-tricalcium phosphate (β-TCP) for the purpose of regenerative therapy around teeth.[3] This combined approach capitalizes on the ability of this highly purified recombinant growth factor to enhance formation of new bone, cementum, and periodontal ligament while fully utilizing the scaffolding properties of this synthetic graft.[27] A prospective, randomized controlled multicenter study has provided compelling evidence that this combined approach enhances clinical regeneration versus the carrier alone.[3] Moreover, a human histologic study[27] provided proof-of-principle evidence that this combined approach is capable of achieving periodontal regeneration. In this latter study, however, the authors also interpreted the histologic findings to suggest that the β-TCP carrier appeared to inhibit new bone formation.

Other human histologic studies, when critically evaluating regenerative outcomes, demonstrate a similar tendency for nonhuman grafts to exhibit seemingly limited osteoconductive activity around teeth[28,29]; in contrast, bone allograft—either alone[22] or in combination with growth factors[21,30]—appears effective in achieving periodontal regeneration. Consistent with histologic studies, cell culture experiments reveal that allografts are highly conductive for human periodontal ligament fibroblasts and exceed the ability for alloplasts to provide this same property.[31] A major clinical concern with DFDBA, therefore, has been its tendency to collapse beneath the flap, leading to diminished space maintenance.

A recent case series study has demonstrated that substantial periodontal regeneration can be achieved when combining recombinant human PDGF-BB (rhPDGF-BB) with FDBA.[32] Moreover, in vitro evidence suggests that this combined scaffold-biologic approach supports human periodontal ligament attachment and spreading.[33] The purpose of this retrospective case series analysis was to provide further clinical information on this same combined approach.

Method and materials

A retrospective chart review was conducted in the private practices to identify patients who had undergone treatment of intraosseous defects using a combination of rhPDGF-BB and FDBA. All patients had been referred to practices limited to periodontics for evaluation and treatment of their periodontal and implant needs. All patients were in good systemic health and underwent initial therapy in either the office of their general dentist or periodontist. Plaque control orientation was performed in the periodontal practice until an excellent level was achieved, with deposits being either absent or minimal. Occlusal therapy consisted of either adjusting or splinting of teeth to reduce excessive mobility or fremitus patterns. Examination included assessments of periodontal probing depth (PD) and clinical attachment level (CAL). PD represented the greatest distance from the free marginal gingiva to the base of the pocket, whereas CAL measured the distance from the cementoenamel junction, crown, or restoration margin to the base of the pocket. All measurements were performed with a Williams probe with UNC markings (Hu-Friedy).

Patients rinsed immediately prior to the surgery with a 0.12% chlorhexidine mouthwash. All measurements were performed using a calibrated 15-mm-long probe and were rounded to the nearest millimeter. Although not calibrated, the surgeons followed essentially the same protocol of flap, root, defect, and postoperative management for the patients. A sulcular incision with a full-thickness flap was employed, and preservation of papillae was attempted in areas where the lesion occurred between teeth. Defects were thoroughly debrided, and the roots scaled and planed with ultrasonic and hand instruments.

Rotary high-speed instrumentation with flame-shaped finishing burs (Brasseler) was used for additional root debridement. If large ledges or exostoses were present in the surgical area, they were removed or reduced through osteoplasty to aid in primary closure. A tetracycline solution was applied to the roots with moistened cotton pellets for further debridement by vigorously rubbing the roots for 2 minutes. This solution was formulated by dissolving a 250-mg capsule into 5 mL of sterile water. The roots were subsequently rinsed with sterile water and intramarrow penetration was performed in the defects to enhance the blood supply to the site. Immediately afterward, the purified protein PDGF-BB (Osteohealth) was applied to the roots while carefully isolating the site from any blood or salivary contamination. Prior to root preparation with tetracycline, the FDBA (LifeNet Health) was reconstituted with PDGF-BB by adding enough of the purified solution to minimally wet the graft particles. This material was introduced into the lesion and placed with light incremental pressure to fill or slightly overfill the lesion. A collagen wound dressing (CollaTape, Zimmer) saturated with PDGF-BB was placed over the graft in interproximal areas. Flaps were positioned over the grafted areas to obtain primary closure and were secured with monofilament polytetrafluoroethylene sutures.

Patients were administered 1 g amoxicillin immediately postoperative, then 875 mg twice daily for the next 7 days. Patients allergic to amoxicillin were prescribed 500 mg azithromycin on the first day and 250 mg per day for the next 4 days. Patients were seen approximately every 10 days for postoperative treatment during the first month. Sutures were removed at either the first or second visit. Patients were then seen every other week for the second and third months and then at 6 months postsurgery. Postoperative visits included plaque debridement, polishing to remove stains, and oral hygiene reinforcement. Patients used 0.12% chlorhexidine mouthwash for postoperative plaque management for the first 30 days by topically swabbing the area. After the first 30 days, patients began rinsing with an essential oil mouthrinse twice per day. Patients were instructed to neither brush nor floss the surgical area for the first 30 days to allow for wound quiescence and stabilization of the clot. Reexamination of PD and CAL was performed 6 months postsurgery. In two patients, flap reflection exposed the regenerative sites during implant placement.

Results

A total of 50 patients (21 men, 29 women) were treated in this case series. The mean age was 51.7 ± 10.8 years (range, 27 to 77 years). Mean CAL at pretreatment was 7.9 ± 1.6 mm (range, 6 to 14 mm), whereas mean PD was 7.8 ± 1.4 mm (range, 6 to 11 mm). At 6 months postsurgery, the mean CAL had

Table 1 Mean pretreatment and 6-month data for intrabony defects treated with FDBA combined with PDGF

	Pretreatment	6 mos	Change from pretreatment
CAL	7.9 ± 1.6	3.9 ± 1.4	4.1 ± 1.3*
PD	7.8 ± 1.4	3.0 ± 1.2	4.8 ± 1. 4*

CAL = clinical attachment level; PD = probing depth.
*$P < .0001$, paired Student *t* test.

Fig 1a *Pretreatment radiograph showing an advanced osseous lesion on the distal aspect of the mandibular left canine. CAL and PD measured 10 mm.*

Fig 1b *Exposure of the lesion after flap reflection and scaling and root planing. The advanced lesion is a combination of one and two walls.*

Fig 1c *After root modification with tetracycline and application of PDGF-BB, the graft (FDBA) hydrated with PDGF was placed into the defect and subsequently covered by a collagen wound dressing.*

Fig 1d *Site sutured with monofilament expanded polytetrafluoroethylene.*

Fig 1e *Healing at the 6-month reentry when implants were placed in the molar region. PD was now 2 mm and CAL measured 4 mm.*

Fig 1f *Substantial defect fill was achieved with hard tissue.*

been reduced to 3.9 ± 1.4 mm (range, 1 to 7 mm), demonstrating improvement of 4.1 ± 1.3 mm. Similarly, mean PD was reduced to 3.0 ± 1.2 mm (range, 1 to 7 mm), reflecting a decrease in probing of 4.8 ± 1.4 mm. The observed improvement in CAL and reduction in PD observed at 6 months, when compared to pretreatment, were statistically significant (Student *t* test, $P < .0001$; Table 1). In the two patients requiring reentry, robust hard tissue fill indistinguishable from the original native bone was noted in each instance. Figure 1 demonstrates the bone fill seen in one of the two reentered defects.

Fig 2a (above left) *Pretreatment radiograph of an advanced osseous lesion at the mesial aspect of a maxillary left first premolar in a 51-year-old man with CAL and PD measurements of 10 mm.*

Fig 2b (above right) *The exposed lesion was a combination of one and two walls and was scaled and root planed.*

Fig 2c *After root treatment with tetracycline and subsequent PDGF, the FDBA-PDGF graft was placed into the defect.*

Fig 2d *Suturing of the site with primary closure was achieved using expanded polytetrafluoroethylene.*

Fig 2e *At 6 months, CAL and PD both measured 4 mm.*

Fig 2f *Radiograph at 6 months suggests that the substantial hard tissue fill of the defect accounts for the improvement in CAL and PD.*

Discussion

The information from this case series suggests that the combined use of bone allograft with PDGF-BB can significantly improve the clinical parameters in teeth with advanced intrabony lesions. The amount of improvement in CAL and reduction in PD were both statistically significant and clinically meaningful (Fig 2, Table 1). The substantial reductions in PD and gain in CAL not only facilitated future periodontal maintenance efforts, but also improved the prognosis of these teeth with advanced disease. The substantial bone fill observed in this retrospective case series duplicates the outcomes reported by Nevins et al[32] using this treatment approach. Although the present findings are consistent with periodontal regeneration, histologic evaluation will be necessary to characterize the true nature of the regenerative outcome using this combination. Attachment and spreading of human periodontal ligament fibroblasts appears more robust when using bone allograft compared to other bone replacement graft materials, and PDGF-BB functions as a powerful mitogen, further enhancing the possibility for periodontal regeneration.[33]

Many of the recent studies that have combined a graft with a biologic agent have incorporated either an alloplast or DFDBA.[3,34] The choice of scaffolding material may hold great significance to the final treatment outcome. Considerations that must be taken into account include space maintenance, biologic compatibility, safety, and ease of use. FDBA was selected rather than β-TCP, which is supplied by the manufacturer, for several reasons. First, Ridgway et al[27] demonstrated that while the combination of β-TCP and PDGF-BB was able to achieve regeneration, there appeared to be an inhibitory effect of this carrier with bone formation, suggesting that the PDGF-BB was the cause of the regeneration. Second, bone allografts have demonstrated the ability to act as a highly effective scaffold for human periodontal ligament fibroblasts when compared to alloplasts and xenograft, which should enhance regeneration.[31] Finally, the mineral content of FDBA allows this graft to effectively maintain space, further enhancing the potential to achieve robust results.

The decision on whether to use DFDBA or FDBA is difficult. Nevins et al[30] have demonstrated the combination of rhPDGF-BB and DFDBA to be regenerative in human furcations, whereas Nevins et al[32] demonstrated that the combination of FDBA and rhPDGF-BB supported robust bone formation in intrabony defects in a case series. Unfortunately, histology was not performed to qualitatively confirm the results achieved in the latter case series. Both bone allografts have similar capabilities to facilitate the attachment and spreading of human periodontal ligament fibroblasts.[31,33] A clinician's selection of allograft, therefore, will depend on whether the lesion is well contained or will require scaffolding for optimal results.[35] In combination, wide, and one-wall noncontaining defects, a mineralized graft such as FDBA may provide better space maintenance and therefore be the graft of choice, whereas in a furcation or two- or three-wall well-contained lesion, DFDBA should warrant strong consideration. These strategies do not include a barrier that may aid in containment but reduce the ability of the periosteum to provide bone progenitor cells.[36,37]

Finally, while this therapeutic approach has demonstrated excellent clinical outcomes, the need for stringent postsurgical maintenance was considered critical in achieving substantial clinical gains. Studies have demonstrated that optimal outcomes with regenerative care are only obtained under optimal plaque control conditions.[38,39] For this reason, a regimen of frequent postsurgical visits and a systemically administered antibiotic were used to facilitate plaque control.[11] With the added periodontal support and reduced probing depths, which facilitate maintenance care, the prognosis of the teeth would be anticipated to improve.

Conclusion

This case series documents the ability for the combined use of rh-PDGF and FDBA to substantially improve the clinical parameters of teeth with advanced periodontal lesions. Prospective controlled studies appear warranted to establish the comparative clinical effectiveness of this therapeutic approach and the histologic nature of the regenerative outcomes.

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