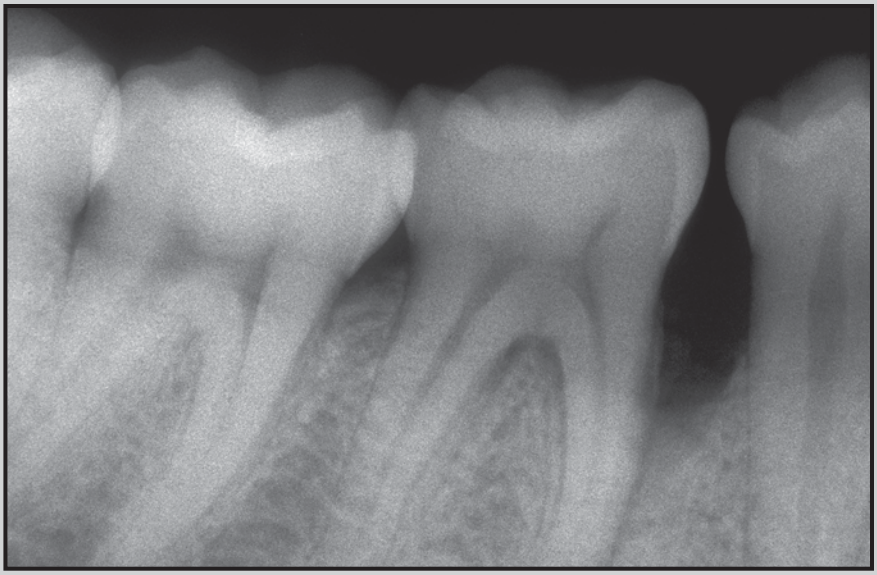
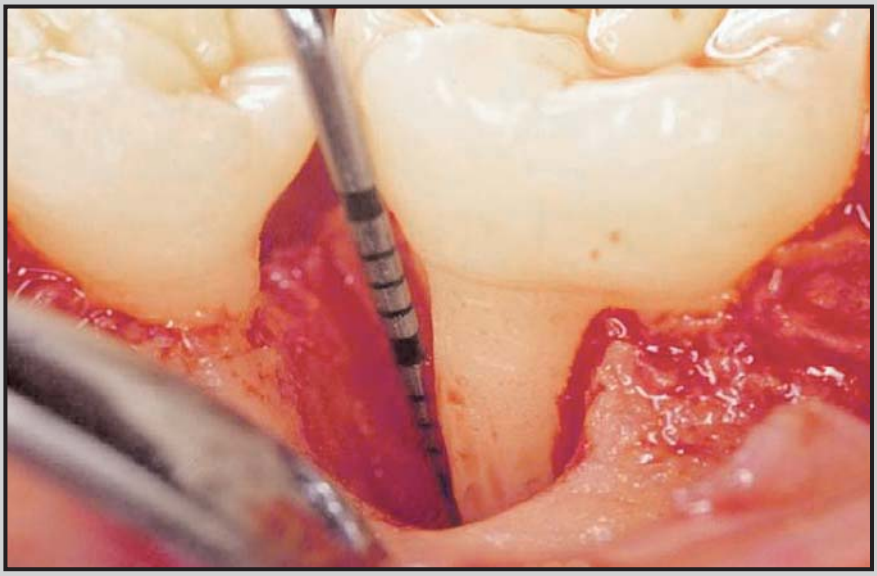
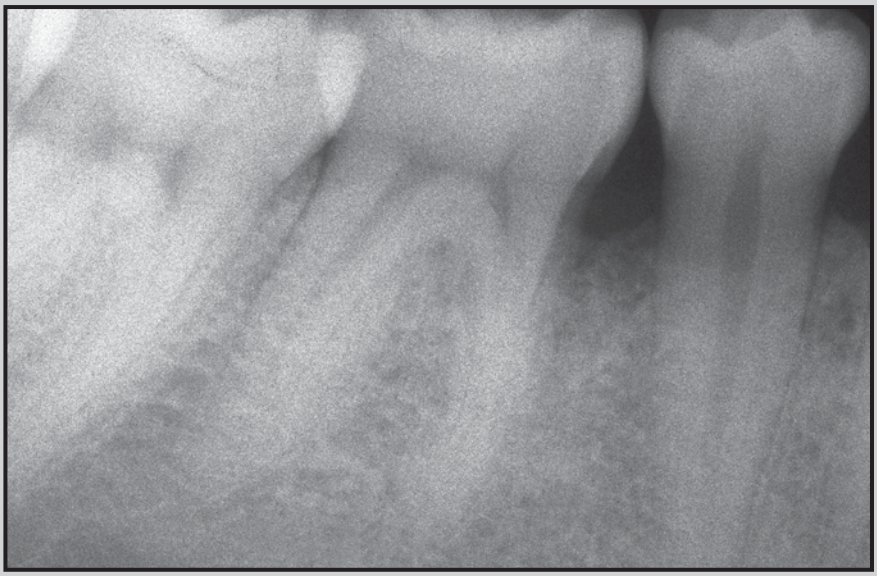
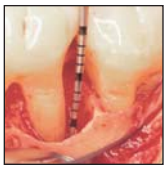






# rhPDGF-BB Promotes Healing of Periodontal Defects: 24-Month Clinical and Radiographic Observations



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*Myron Nevins, DDS***/Samuel E. Lynch, DMD, DMSc*****

*A new therapeutic system using purified recombinant human platelet-derived growth factor-BB (rhPDGF-BB) in combination with a biocompatible, osteoconductive, synthetic scaffold beta-tricalcium phosphate (β-TCP) has recently been shown in a large-scale, prospective, blinded, randomized clinical trial to safely and effectively treat advanced periodontal osseous defects. A significant gain in clinical attachment level was observed 3 months postsurgery for sites treated with 0.3 mg/mL rhPDGF-BB + β-TCP versus β-TCP + buffer (active control), with this trend continuing at 6 months postsurgery. Additionally, sites treated with 0.3 mg/mL rhPDGF-BB + β-TCP also had significantly greater radiographic linear bone gain and percent defect fill at 6 months postsurgery than sites that received bone substitute with buffer. Representative cases from the clinical trial were followed to assess their ability to maintain the initial effect of treatment observed at 6 months. At 18 or 24 months postsurgery, with the same clinical and radiographic measurement techniques used as were performed at the 6-month time point for the clinical trial, these cases demonstrated maintenance of the clinical attachment level for all but one case, with all cases demonstrating substantial increases in linear bone gain and percent bone fill versus measurements obtained at 6 months postsurgery. Substantial radiographic changes in the appearance of the defect fill were observed for both rhPDGF-BB treatment groups, consisting of increased radiopacity and bone trabeculation, indicative of increased mineralization and maturation of the bone observed 6 months postsurgery.* (Int J Periodontics Restorative Dent 2006;26:223–231.)

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Recombinant human platelet-derived growth factor-BB (rhPDGF-BB) is a well-characterized tissue growth factor that has been shown, in animals and humans, to be mitogenic and chemotactic for periodontal ligament and bone cells, with the additional effect of promoting regeneration of bone, ligament, and cementum.[1–16] An initial human clinical trial showed that application of 0.15 mg/mL of rhPDGF-BB and 0.15 mg/mL recombinant human insulin-like growth factor I resulted in a significant improvement in bone fill in periodontal defects compared to conventional surgery plus a vehicle control.[17] Additionally, results of a pilot human trial indicated that application of 0.5 to 1.0 mg/mL rhPDGF-BB in allograft resulted in regeneration of bone, ligament, and cementum, as demonstrated by blinded histologic evaluation.[2,18]

A new therapeutic system using purified rhPDGF-BB in combination with a biocompatible, osteoconductive, synthetic scaffold (beta-tricalcium phosphate [β-TCP]) has recently been evaluated in a large-scale, prospective, blinded, randomized clinical trial for its ability to safely and effectively treat

advanced periodontal osseous defects.[19] The purpose of this report is to present representative cases from the clinical trial for this new therapeutic system, for the period of enrollment through 24 months posttreatment. Extensive clinical and radiographic documentation, including clinical attachment level (CAL) measurements and radiographic percent bone fill (%BF) as well as linear bone gain (LBG), are presented for each case beyond the initial study period of 6 months to provide longer follow-up information related to maintenance of the initial results.

## Method and materials

As reported earlier,[19] in the 180-patient clinical trial designed to evaluate this new therapeutic system for the treatment of intrabony periodontal defects (≥ 4 mm) patients were randomly placed into one of three treatment groups: *(1)* β-TCP + 0.3 mg/mL rhPDGF-BB in buffer; *(2)* β-TCP + 1.0 mg/mL rhPDGF-BB in buffer; and *(3)* β-TCP + buffer (active control). Safety data were assessed by the frequency and severity of adverse events. Effectiveness measurements included CAL and gingival recession (GR), measured clinically, as well as LBG and %BF, as assessed radiographically by an independent centralized radiology review center. All participants were masked with respect to treatment group.

Briefly, the results demonstrated a significant gain in CAL at 3 months for group 1 compared to group 3 (3.8 versus 3.3 mm; $P = .032$), with this trend continuing at 6 months, although the difference was not statistically significant ($P = .11$). Group 1 sites also had significantly greater LBG (2.6 versus 0.9 mm, respectively; $P < .001$) and %BF (57% versus 18% respectively; $P < .001$) than group 3 sites at 6 months. No serious adverse events were attributable to any of the treatments.

This study demonstrated that the use of rhPDGF-BB was safe and effective in the treatment of osseous periodontal defects and that treatment with rhPDGF-BB stimulated a significant increase in the rate of CAL gain, reduced GR at 3 months postsurgery, and improved bone fill as compared to a TCP bone substitute at 6 months.

The ability to maintain the initial effect of treatment observed at 6 months was evaluated at 12 and 24 months posttreatment using the same clinical and radiographic measurement techniques that were performed at the 6-month time point. Representative patients from the study are presented.

## Results

### *Patient 1*

The patient, a 61-year-old nonsmoking Hispanic woman, presented with radiographic evidence of bone loss on the distal surface, as well as in the area of the furcation, of the mandibular left first molar (Fig 1a). Clinical probing depth (PD) and attachment levels of 8 and 11 mm, respectively, were observed at baseline. The associated bone defect measured 5 mm deep distobuccally, 8 mm deep on the direct distal side, and 3 mm mesiodistally (Fig 1b). Surgery was performed following the study protocol; this case was ran-

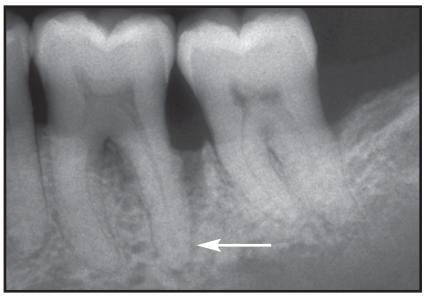
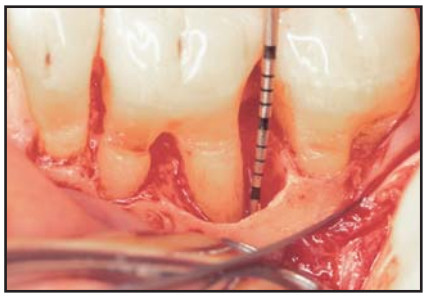


**Fig 1a** (left) *Baseline periapical radiograph of patient #1 showing bone loss on the distal surface of the mandibular left first molar (arrow) that extends into the area of the furcation.*

**Fig 1b** (right) *Intraoperative buccal view of the circumferential intrabony defect.*



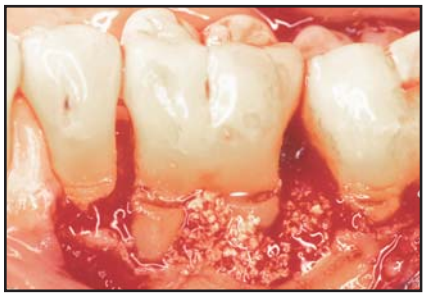
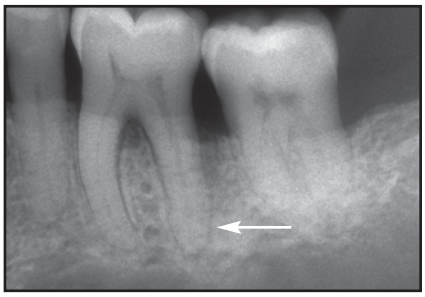


**Fig 1c** (left) *Intraoperative view of surgical site following placement of 0.3 mg/mL rhPDGF-BB + β-TCP.*

**Fig 1d** (right) *Bone fill distally and in the area of the furcation at 6 months postsurgery.* Arrow *marks base of original defect.*



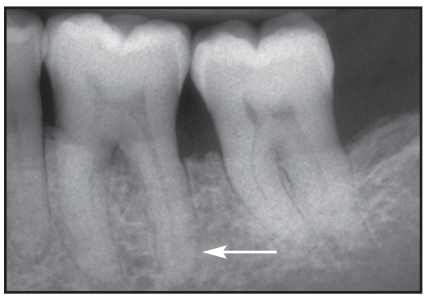
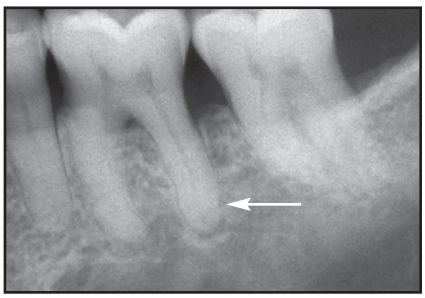


**Fig 1e** (left) *At 12 months, demonstration of extensive bone fill distally and in the furcation of the mandibular left first molar. Bone trabeculation and a well-defined lamina dura are evident.* Arrow *marks base of original defect.*

**Fig 1f** (right) *Bone fill of the distal and furcal components of the original defect at 24 months. Crestal cortication is evident, along with a distinct lamina dura along the distal root surface.* Arrow *marks base of original defect.*



domized to receive 0.3 mg/mL rhPDGF-BB + β-TCP (Fig 1c).

At 6 months postsurgery, PD and CAL measurements were 3 and 6 mm, respectively, representing a 5-mm improvement from baseline measurements. Increased radiopacity was observed on the distal surface of the tooth (Fig 1d), although the area of the furcation had not changed significantly from baseline. %BF on the distal surface of the tooth was calculated to be 81%, with an LBG of 5.11 mm.

At 12 months postsurgery, PD and CAL remained unchanged from 6 months postsurgery. Increased radiopacity, with a distinct pattern of trabeculation, was observed in the area of the original defect on both the distal surface of the root as well as in the area of the furcation. The %BF was 94.3%, with an LBG of 5.97 mm (Fig 1e).

At 24 months postsurgery, PD and CAL remained unchanged from 6 months postsurgery. Radiographic bone fill continued to progress from observations made at 12 months, with increased crestal cortication and a pattern of bony trabeculation, indicative of bone maturation (Fig 1f). These clinical and radiographic observations were further supported by the calculated %BF of 89% and an LBG of 5.62 mm.

## *Patient 2*

The patient, a 55-year-old Caucasian woman and smoker for 40 years, presented with radiographic evidence of bone loss on the mesial surface of the mandibular right first molar extending into the area of the furcation (Fig 2a). A clinical PD of 9 mm and CAL of 11

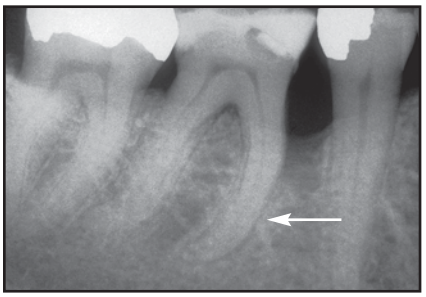


**Fig 2a** (left) *Baseline periapical radiograph of patient #2 showing bone loss on the mesial root surface of the mandibular right first molar* (arrow) *that extends into the area of the furcation.*

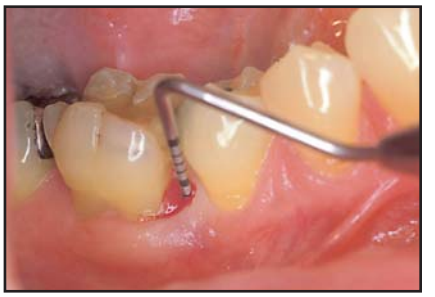


**Fig 2b** (right) *Baseline clinical measurement on the mesial surface of the mandibular right first molar.*

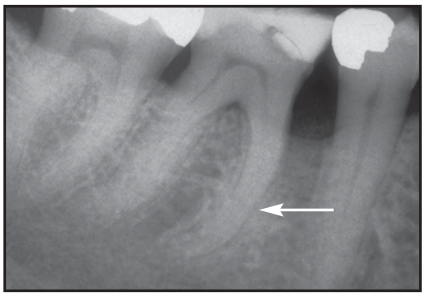


**Fig 2c** (left) *Treated site at 3 months postsurgery showing diffuse, slightly radiopaque fill of the original mesial defect* (arrow *marks base of original defect) and small residual radiolucency at the fornix of the furcation.*

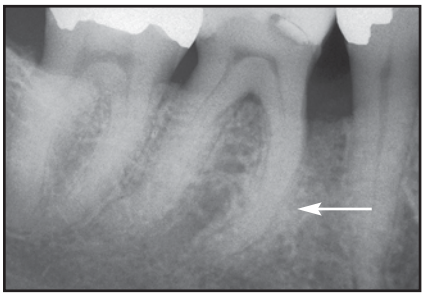


**Fig 2d** (right) *At 6 months postsurgery, mesial bone fill has increased both in height and density, with discrete areas of trabeculation present.* Arrow *marks base of original defect.*

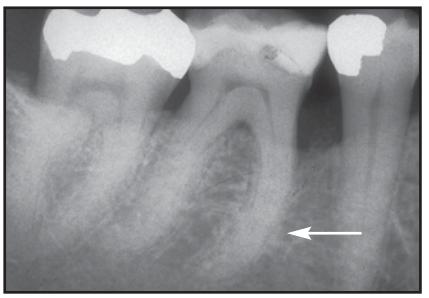


**Fig 2e** (left) *Further bone fill of the original mesial defect at 12 months, with further maturation (trabeculation).* Arrow *marks base of original defect.*

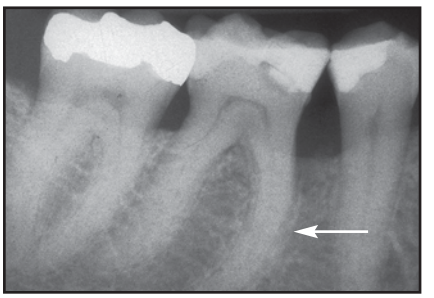


**Fig 2f** (right) *At 24 months, complete fill of the furcation and the area of the original mesial defect. The bone fill is contiguous with the surrounding bone.* Arrow *marks base of original defect.*

mm were observed at baseline (Fig 2b). During surgery, a 7-mm-deep by 3-mm-wide (mesiodistally) two- and three-walled intrabony defect on the mesiolingual surface of the tooth was revealed. Surgery was performed following the study protocol, with this case receiving 0.3 mg/mL rhPDGF-BB + β-TCP.

At 3 months postsurgery, there was increased radiopacity in the area of the original defect, although it was uniform in appearance without any discernible pattern of bony trabeculation (Fig 2c). At 6 months, PD and CAL were 3 and 5 mm, respectively. Increased radiopacity was apparent in the area of the furcation as well as on the mesial surface of the root, with isolated areas exhibiting a pattern of bony trabeculation not observed at 3 months (Fig 2d). %BF on the mesial was calculated to be 65%, with an LBG of 4.11 mm.

At 12 months, PD and CAL remained unchanged from 6 months. Radiographic examination revealed increased radiopacity in the area of the original defect, which was calculated to be 75% BF with an LBG of 4.79 mm (Fig 2e).

At 24 months, PD and CAL remained unchanged. The 6-mm improvement in CAL from baseline measurements was further supported by radiographic findings, which demonstrated increased bone fill and a pattern of trabeculation indicative of mature bone (Fig 2f). The area of the furcation was totally radiopaque in appearance, indicating the presence of mineralized tissue throughout the furcation. These clinical and radiographic improvements were supported by the calculated %BF of 99% and an LBG of 6.29 mm.

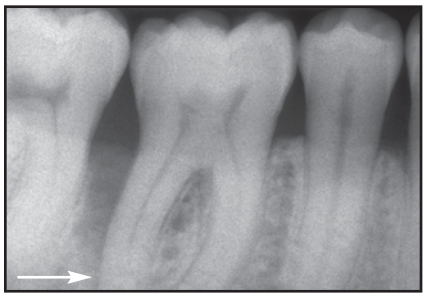


**Fig 3a** (left) *Baseline periapical radiograph of patient #3 showing distal bone loss (arrow) on the mandibular right first molar extending into the area of the furcation.*

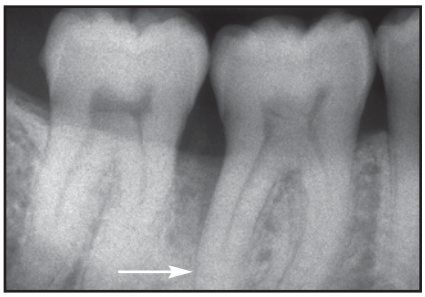


**Fig 3b** (right) *Six-month postsurgical bone fill of the distal and furcal components of the original defect.* Arrow *marks base of original defect.*

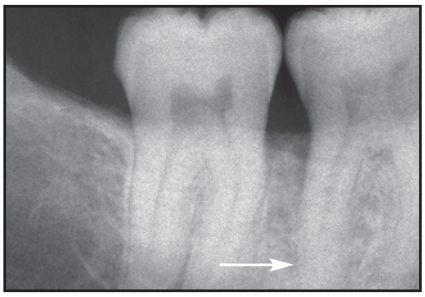


**Fig 3c** (left) *Further bone fill and increased radiopacity (bone density) at 12 months.* Arrow *marks base of original defect.*

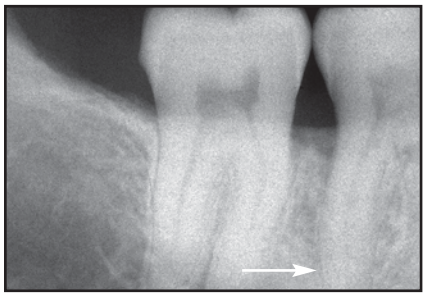
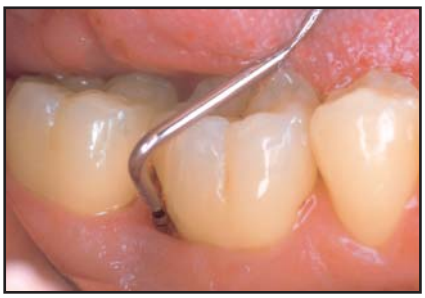
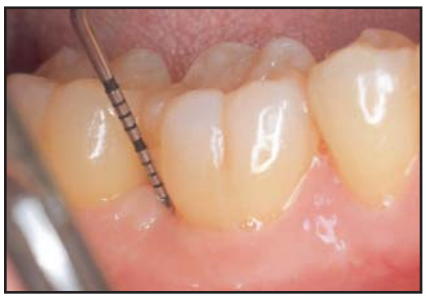


**Fig 3d** (right) *At 24 months, the bone fill height observed at 12 months has been maintained, with further increases in density and maturity (trabeculation). The furcation appears to be completely filled with bone.* Arrow *marks base of original defect.*



**Figs 3e and 3f** *Clinical measurements (buccal view) (e, left) at baseline and (f, right) at 24 months postsurgery.*



*Patient 3*

The patient, a 38-year-old nonsmoking Caucasian man, presented with radiographic evidence of bone loss on the distal root surface of the mandibular right first molar that extended into the furcation (Fig 3a). Baseline PD and CAL of 13 mm were observed. Upon surgical exposure, a 7-mm-deep by 4-mm-wide (mesiodistally) two- and three-walled intrabony defect was revealed on the distobuccal surface of the tooth. Surgery was performed following the study protocol, with this case receiving 1.0 mg/mL rhPDGF-BB + β-TCP.

At 6 months postsurgery, PD and CAL were 4 mm, representing a 9-mm gain in CAL from baseline. Increased radiopacity was demonstrated in the area of the furcation as well as on the distal surface of the tooth (Fig 3b). %BF was calculated to be 46.2%, with an LBG of 4.98 mm.

At 12 months, progression and maturation of bone fill continued in both the furcation and the distal defect, as evidenced by increased radiopacity within the defect and a pattern of bone trabeculation not previously observed. %BF on the distal surface of the tooth was calculated to be 64.2% with an LBG of 7.0 mm (Fig 3c).

At 24 months, radiographic evidence of bone fill continued to increase from observations made at 12 months, with increased radiopacity in the area of the original defect and a pattern of bony trabeculation indicative of further bone maturation (Fig 3d). PD and CAL remained unchanged from the 6- and 12-month measurements, with a significant improvement from baseline (Figs 3e and 3f). These clinical and radiographic improvements are supported by the calculated %BF of 77% and the LBG of 8.44 mm.

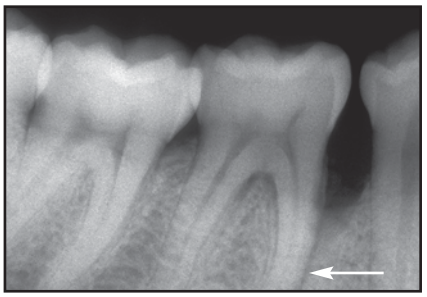


**Fig 4a** (left) *Baseline periapical radiograph of patient #4 demonstrating bone loss* (arrow) *on the mesial root surface of the mandibular right first molar with incipient bone loss in the area of the furcation.*

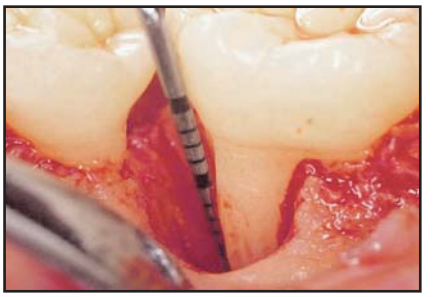


**Fig 4b** (right) *Intraoperative lingual view of the affected tooth showing a deep, wide intrabony defect on the mesial root surface.*

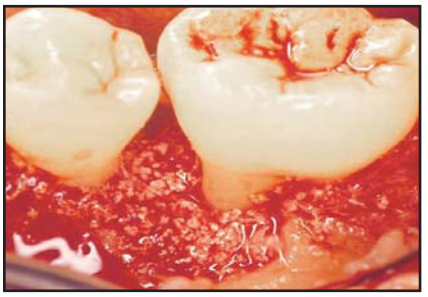


**Fig 4c** (left) *Intraoperative lingual view of the tooth following placement of 0.3 mg/mL rhPDGF-BB + β-TCP.*

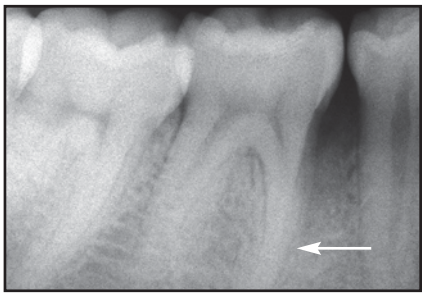


**Fig 4d** (right) *Diffuse, slightly radiopaque fill of the mesial defect at 6 months postsurgery.* Arrow *marks base of original defect.*

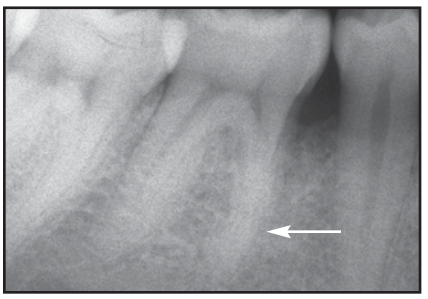


**Fig 4e** *At 18 months, the area of the furcation is completely filled, and the mesial defect fill has increased both in height and density compared with 6-month measurements.* Arrow *marks base of original defect.*

*Patient 4*

The patient, a 31-year-old nonsmoking African American man, presented with radiographic evidence of bone loss on the mesial surface of the mandibular right first molar, with incipient bone loss in the area of the furcation (Fig 4a). PD and CAL of 11 mm were observed at baseline. Upon surgical exposure, a bone defect was revealed that measured 10 mm deep mesiobuccally, 12 mm deep on the direct mesial side, and 4 mm mesiodistally (Fig 4b). Surgery was performed following the study protocol, with this case randomized to receive 0.3 mg/mL rhPDGF-BB + β-TCP (Fig 4c).

At 6 months postsurgery, PD and CAL were 4 mm, a 7-mm improvement from baseline. Increased radiopacity was seen on the mesial surface of the tooth, although the radiopacity lacked an organized, trabecular bone pattern (Fig 4d). %BF in the area of the original mesial defect was calculated to be 93%, with an LBG of 5.36 mm.

At 18 months, PD and CAL measured 3 and 6 mm, respectively, representing 8- and 5-mm improvements from baseline measurements. Radiographic evidence of bone fill continued to increase from observations made at 6 months, with increased radiopacity in the area of the original defect and a pattern of bony trabeculation indicative of mature bone (Fig 4e). Radiographic LBG was 5.43 mm, for a calculated %BF of 88%.

**Table 1** Results of four cases treated with rhPDGF-BB + β-TCP

| | Time of evaluation | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | 6 months | | | | 12 months | | | | 24 months | | | |
| Case/ treatment group | PD (mm) | CAL (mm) | PD (mm) | CAL (mm) | LBG (mm) | %BF | PD (mm) | CAL (mm) | LBG (mm) | %BF | PD (mm) | CAL (mm) | LBG (mm) | %BF |
| 1 (1.0 mg/mL rhPDGF-BB + β-TCP) | 13 | 13 | 4 | 4 | 4.98 | 46 | 6 | 5 | 7.0 | 64 | 4 | 4 | 5.62 | 89 |
| 2 (0.3 mg/mL rhPDGF-BB + β-TCP) | 9 | 11 | 3 | 5 | 4.11 | 65 | 3 | 5 | 4.79 | 75 | 3 | 5 | 6.29 | 99 |
| 3 (0.3 mg/mL rhPDGF-BB + β-TCP) | 8 | 11 | 3 | 6 | 5.11 | 81 | 3 | 6 | 5.97 | 94 | 3 | 6 | 8.44 | 77 |
| 4 (0.3 mg/mL rhPDGF-BB + β-TCP) | 11 | 11 | 4 | 4 | 5.36 | 93 | NA | NA | NA | NA | 3* | 6* | 6.72* | 88* |

*Measurements are from 21 months postsurgery, not 24 months.
PD = probing depth; CAL = clinical attachment level; LBG = linear bone gain; %BF = % bone fill; NA = not available.

## Discussion

This article presents the long-term results of four representative cases from a large-scale, prospective, blinded, randomized clinical trial designed to evaluate a new therapeutic system using rhPDGF-BB in combination with β-TCP for the treatment of intrabony periodontal defects.

The initial report of results from the trial[19] demonstrated that the use of rhPDGF-BB was safe and effective in the treatment of intrabony periodontal defects and that rhPDGF-BB stimulated a significant increase in the rate of CAL gain, reduced GR at 3 months postsurgery, and improved bone fill as compared to the β-TCP bone substitute at 6 months.

The long-term results (12 and 21 or 24 months postsurgery) of representative cases from the trial illustrate maintenance of the initial 6-month clinical results and substantial improvement of the 6-month radiographic results.

In both rhPDGF-BB treatment groups, the CAL measurements were maintained in most cases, and all cases demonstrated an increase in radiographic %BF and LBG measurements (Table 1).

Important observations related to the radiographic results for all rhPDGF-BB cases were also noted. For the period between 6 and 12 months (or 21 months for patient #4), there were notable changes in the appearance of the defect fill. In addition to increased radiopacity of the defect fill, a bony trabecular pattern became more evident, indicative of the bone maturation process during which host bone continues to be deposited and mineralized and the synthetic bone matrix is replaced. This pattern continued throughout the remaining 9- to 12-month observation period, with a "blending" of the defect fill and bone surrounding the original defect. This finding is important because it provides surgeons with important information related to expectations at various time points following surgical treatment using the new therapeutic system.

The current case series illustrates that gains in CAL following treatment with rhPDGF-BB + β-TCP are stable, and radiographic %BF and LBG may be expected to increase substantially following the initial 6-month postsurgical observation.

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