Treatment of Chronic Periodontitis with Recombinant Human Fibroblast Growth Factor-2 and Deproteinized Bovine Bone Mineral in Wide Intrabony Defects: 12-month Follow-up Case Series

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Abstract

Clinical use of 0.3% recombinant human fibroblast growth factor (rhFGF)-2 for periodontal regeneration received formal approval in Japan in 2016. The combination of growth factor and bone graft material is used to enhance periodontal healing in regenerative therapy. The exact effects of combination therapy on periodontal healing remain unknown, however. Here, we report three cases of chronic periodontitis treated with the combination of rhFGF-2 and deproteinized bovine bone mineral (DBBM). Following initial periodontal therapy, periodontal regenerative therapy using rhFGF-2 in combination with DBBM was performed to treat wide intrabony defects. Periodontal parameters and radiographic bone fill were reevaluated at 3 months, 6 months, and 1 year postoperatively. Oral health-related quality of life (OHRQL) was assessed as a patient-reported measure of outcome. At 1 year postoperatively, probing pocket depth and clinical attachment level showed a significant improvement in comparison with at baseline. An improvement was also noted in radiographic evidence of bone fill and total OHRQL scores. Combination therapy yielded clinically favorable results in the present cases.

Key words: Periodontal regenerative therapy — Recombinant human fibroblast growth factor-2 — Deproteinized bovine bone mineral — Intrabony defects

Introduction

Periodontitis affects tooth supporting structures, eventually leading to tooth loss. Tooth loss can exert a serious effect on quality of life (QOL) due to a range of problems, including in speech and esthetics. The goal of periodontal therapy is to reduce tissue inflammation and, ultimately, achieve regeneration of lost periodontal tissues. In periodontal tis
sue engineering, a number of factors must be taken into consideration, such as the appropriate cells, biological signals, scaffolds, blood supply, mechanical loading, and microbial control\(^\text{19}\). Numerous studies have investigated the effect of periodontal regenerative therapies such as guided tissue regeneration and the use of enamel matrix derivative (EMD), with most reporting various degrees of clinical success\(^\text{5,18,28}\).

Use of 0.3% recombinant human fibroblast growth factor (rhFGF-2) for periodontal regeneration received formal approval in Japan in 2016\(^\text{20}\). Recombinant human fibroblast growth factor-2 stimulates proliferation, differentiation, and angiogenesis in a variety of cells, and has been reported to be effective in regenerating periodontal tissue in animal models\(^\text{14,27}\). Previous in vivo studies from our research group showed that rhFGF-2 enhances periodontal healing\(^\text{1,7,25}\).

Scaffolds provide a template structure to support and facilitate essential processes in periodontal regeneration\(^\text{26}\). The combination of EMD and deproteinized bovine bone mineral (DBBM) resulted in greater improvement in hard tissue than treatment with EMD alone\(^\text{31}\). Furthermore, one randomized controlled clinical trial showed that the use of rhFGF-2 resulted in a greater degree of radiographic evidence of bone fill than the use of EMD in intrabony defects\(^\text{11}\). Recently, our research group showed that the combined use of rhFGF-2 and DBBM yielded an enhanced radiographic outcome compared to rhFGF-2 alone at 6 months postoperatively in the treatment of intrabony defects\(^\text{30}\). These findings suggest that combination therapy with rhFGF-2 and DBBM is an effective treatment modality. Here, we present three cases that illustrate treatment of wide intrabony periodontal defects with the combination of rhFGF-2 and DBBM.

### Case Presentation

These cases form part of a clinical study investigating longitudinal clinical outcome in regenerative therapy with rhFGF-2 and DBBM which was approved by the Ethics Committee of Tokyo Dental College (No.747). Written informed consent was obtained from the patients for study participation and inclusion in this report.

1. **Case 1**

In June 2015, a 48-year-old woman visited our hospital (Tokyo Dental College Suidobashi Hospital) with the chief complaint of gingival swelling. On initial examination, gingival inflammation and subgingival calculus were observed in the molar region. Periodontal examination revealed that 30.8% of sites had a probing pocket depth (PPD) of \(\geq 4\) mm and 14.7% one of \(\geq 7\) mm. Bleeding on probing (BOP) was observed at 42.9% of sites. The level of plaque control as assessed by the O’Leary plaque control record (PCR)\(^\text{17}\) was 66.3% (Table 1). Radiographic examination revealed angular bone defects and widening of the periodontal ligament space on the

| Case | First Visit | Post-IP |
|------|------------|---------|
| PPD of \(\geq 4\) mm (%) | 30.8 | 16.7 |
| PPD of \(\geq 7\) mm (%) | 14.7 | 1.4 |
| BOP (%) | 42.9 | 24.3 |
| PCR (%) | 66.3 | 22.9 |

PPD, probing pocket depth; BOP, bleeding on probing; PCR, plaque control record

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### Table 1 Changes in clinical parameters between first visit and post-initial periodontal therapy

| Case 1 | Case 2 | Case 3 |
|--------|--------|--------|
| #16    | #37    | #23    |
| First Visit | Post-IP | First Visit | Post-IP | First Visit | Post-IP |
| PPD of \(\geq 4\) mm (%) | 30.8 | 16.7 | 32.1 | 10.1 | 34.1 | 6.8 |
| PPD of \(\geq 7\) mm (%) | 14.7 | 1.4 | 7.1 | 1.8 | 2.2 | 3.0 |
| BOP (%) | 42.9 | 24.3 | 78.0 | 31.0 | 40.6 | 17.4 |
| PCR (%) | 66.3 | 22.9 | 63.4 | 19.6 | 48.3 | 18.2 |

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The mesial aspect of tooth #16. Periapical radiographs were taken using customized film holders as described previously\(^6\). Assessment of radiographic bone fill (RBF) at the surgical sites was performed using a method previously described\(^24\). The patient’s oral health-related QOL (OHRQL) was assessed as a measure of patient-reported outcome\(^21\). The total OHRQL score was 23. The clinical diagnosis was moderate chronic periodontitis. A treatment plan was presented to the patient and her consent to the proposed plan obtained.

2. Case 2

In April 2016, a 52-year-old man visited our hospital with the chief complaint of gingival swelling and a mobile mandibular incisor. Periodontal examination revealed that 32.1% of sites had a PPD of \(\geq 4\) mm and 7.1% one of \(\geq 7\) mm. Bleeding on probing was observed at 78.0% of sites. The PCR score was 63.4% (Table 1). Radiographic examination showed angular bone defects on the distal aspect of tooth #37. The total OHRQL score was 26. The clinical diagnosis was moderate chronic periodontitis. A treatment plan was presented to the patient and his consent to the proposed plan obtained.

3. Case 3

In November 2016, a 58-year-old woman visited our hospital with the chief complaint of gingival swelling and pain. Gingival inflammation and subgingival calculus were observed in the molar region. Periodontal examination revealed that 34.1% of sites had a PPD of \(\geq 4\) mm and 2.2% one of \(\geq 7\) mm. Bleeding on probing was observed at 40.6% of sites. The PCR score was 48.3% (Table 1). Radiographic examination showed angular bone defect on the distal aspect of tooth #23. The total OHRQL score was 33. The clinical diagnosis was moderate chronic periodontitis. A treatment plan was presented to the patient and her consent to the proposed plan obtained.

### Clinical Procedures and Outcomes

1. Case 1

After initial periodontal therapy, reevaluation revealed a reduction in the PCR score to 22.9%. Sites with a PPD of \(\geq 4\) mm and 7 mm decreased to 16.7% and 1.4%, respectively. The total OHRQL score was 21. At reevaluation, closed pockets were observed in 60.2% of the teeth\(^10,30\) and BOP in 24.3% (Table 1). Changes in clinical and radiographic parameters in the 3 cases are summarized in Table 2. These results were judged to be “incomplete” according to the criteria for the success of non-surgical periodontal therapy\(^20\). In #16, which had a PPD of 6 mm, a wide vertical bone defect was still present, so regenerative

### Table 2  Changes in clinical parameters during treatment

| Case 1 #16 | Case 2 #37 | Case 3 #23 |
|------------|------------|------------|
|            | Pre-op     | 3 M | 6 M | 1 Y | Pre-op | 3 M | 6 M | 1 Y | Pre-op | 3 M | 6 M | 1 Y |
| PPD (mm)   | 6          | 2.5 | 3   | 3   | 8      | 3   | 3   | 3   | 6     | 3.5 | 3.5 | 3   |
| GM (mm)    | 0          | 0.5 | 0.5 | 0.5 | 0      | 0.5 | 0.5 | 0.5 | 1     | 2   | 2   | 2   |
| CAL (mm)   | 6          | 3   | 3.5 | 3.5 | 8      | 4.5 | 3.5 | 3.5 | 7     | 5.5 | 5.5 | 5   |
| BOP        | +          | −   | −   | −   | +      | −   | −   | −   | +     | −   | −   | −   |
| TM         | 1          | 0   | 0   | 0   | 1      | 0   | 0   | 0   | 0     | 0   | 0   | 0   |
| RBF (%)    | −          | 20.0| 40.0| 40.0| −      | 33.3| 44.4| 44.4| −     | 20.0| 60.0| 60.0|

PPD, probing pocket depth; GM, gingival margin; CAL, clinical attachment level; BOP, bleeding on probing; TM, tooth mobility; RBF, radiographic bone fill
therapy with rhFGF-2 and DBBM was performed. The defect was accessed using the papilla preservation technique\(^5,6\). Following removal of granulation tissue and scaling and root planing, 0.3% rhFGF-2 (REGROTH\(^\text{®}\) Dental Kit, 600 µg in hydroxypropyl cellulose; Kaken Pharmaceutical, Tokyo, Japan) and DBBM (Bio-Oss\(^\text{®}\), 0.25–1.0 mm granules; Geistlich Pharma AG, Wolhusen, Switzerland) were applied to the defect. Recombinant human fibroblast growth factor-2 was first applied to the root surfaces (Fig. 1c, 3c, 5c), after which DBBM (pre-treated with FGF-2) was placed in the defects and lightly compressed (Fig. 1d, 3d, 5d) in accordance with a previously reported method\(^7\). The 3-wall defect was 5 mm in depth and 4 mm in width. Prior to application, the rhFGF-2 solution was thoroughly mixed with DBBM in a sterile disposable dish. Immediately after application, the flaps were repositioned for complete closure and sutured with modified vertical mattress or interrupted sutures (Fig. 1).

To assess periodontal healing, PPD, CAL and RBF were reevaluated at 3 months, 6 months and 1 year postoperatively. Additionally, OHRQL was used as a patient-reported measure of outcome.

At the 1-year reevaluation, a PPD of 3 mm and 2.5 mm gain in CAL were found in #16. At 1 year postoperatively, RBF showed an increase to 40.0% in comparison with 20.0% at 3 months postoperatively (Table 2). The periodontal condition remained stable for 1 year (Fig. 2). The total OHRQL score was 13, indicating an improvement in QoL from at first visit (Fig. 7).
2. Case 2

After initial periodontal therapy, reevaluation revealed a reduction in the PCR score to 19.6%. Sites with a PPD of ≥4 mm and 7 mm decreased to 10.1% and 1.8%, respectively. The total OHRQL score was 16. At reevaluation, closed pockets were observed in 69.6% of the teeth and BOP in 31.0% (Table 1). These were judged to be “incomplete” according to the criteria for the success of non-surgical periodontal therapy. In #37, the site with a PPD of 8 mm was still present, and the 2–3-wall defect measured 6 mm in depth and 4 mm in width. The site was treated with regenerative therapy using rhFGF-2 and DBBM (Fig. 3).

At the 1-year reevaluation, a PPD of 3 mm and 4.5 mm gain in CAL were found in #37. At each time point, PPD, CAL, and RBF showed an improvement in comparison with baseline. At 1 year postoperatively, RBF showed an increase to 44.4% in comparison with 33.3% at 3 months postoperatively (33.3%) (Table 2). Additionally, these periodontal conditions were observed to remain stable for 1 year (Fig. 4). The total OHRQL score was 9, indicating an improvement in QoL from at first visit (Fig. 7).

3. Case 3

After initial periodontal therapy, a reduction was observed in the PCR score to 18.2%. Sites with a PPD of ≥4 mm decreased to 6.8%. The total OHRQL score was 28. At reevaluation, closed pockets were observed in 81.3% of the teeth and BOP in 17.4% (Table 1).
These results were judged to be “sufficient” according to the criteria for the success of non-surgical periodontal therapy. However, vertical bone defects were still present in #23. Therefore, we decided to implement surgical treatment with rhFGF-2 and DBBM. The site with a PPD of 6 mm was still present and the 2–3-wall defect measured 4 mm in depth and 3 mm in width. Open flap debridement was implemented for #23 and rhFGF-2 with DBBM applied to the defect (Fig. 5).

At the 1-year postoperative reevaluation, a PPD of 3 mm and 2 mm gain in CAL were found in #23. At each time point, PPD, CAL, and RBF showed an improvement in comparison with at baseline. At 1 year postoperatively, RBF showed an increase to 60.0% in comparison with 20.0% at 3 months postoperatively (Table 2). Additionally, these periodontal conditions were observed to remain stable for 1 year (Fig. 6). The total OHRQL score was 20, indicating an improvement in QoL from at first visit (Fig. 7).

**Discussion**

In an earlier randomized control trial, our research group reported that combination therapy with rhFGF-2 and DBBM enhanced RBF compared with rhFGF-2 alone at 6 months postoperatively\(^ {20}\). However, information is limited concerning longitudinal clinical outcomes with such therapy. It has been reported that application of rhFGF-2 in combination with hyaluronic acid significantly
improved clinical parameters at 1 year after treatment. In the present cases, combination regenerative therapy was selected for the treatment of vertical bone defects. All cases showed an improvement in PPD and a clinically relevant gain in CAL at 1 year when compared with at baseline (Table 2). Additionally, the total OHRQL score was reduced in comparison with at baseline first visit (Fig. 7).

One study of regenerative therapy using EMD reported that there was a 2.5-times higher chance of obtaining a gain in CAL of 4 mm or more with a narrow defect (mean angle of 22°) than with a wider defect (mean angle of 36°). In the present case series, the defects were 2- or 3-wall and were relatively wide (mean defect angle 46°). Therefore, we chose combination therapy with rhFGF-2 and DBBM. Enamel matrix derivative and rhFGF-2 are in gel-like form, and when used alone have no space-making effect. It was expected that the combination of EMD with a graft material might overcome the problem of space maintenance in wider defects. In addition, the guidelines of the Japanese Society of Periodontology recommend using EMD in combination with bone graft material when a given bone defect is estimated to be ≥4 mm in depth and ≥2 mm in width.

In a 9-year case report of a patient with periodontitis, the treatment of one site with rhFGF-2 resulted in greater bone healing than treatment of the contralateral site with EMD. We expected that the combination rhFGF-2 with a bone substitute would enhance healing of the wide intrabony defects seen...
here. Combination therapy with rhFGF-2 and DBBM resulted in an improvement in PPD and a gain in CAL at 1 year in comparison with at baseline (Table 2).

Although combination therapy yielded clinically favorable outcomes, these may give little insight into the patient’s perception regarding the disease and its treatment. Therefore, we introduced the OHRQL as a patient-centered measure of outcome. The OHRQL score showed an improvement after initial periodontal therapy in comparison with at first visit. This finding is consistent with our own previous reports\(^\text{13,21,22}\). This may have been due to the removal of inflammation and improvement in the oral environment with initial periodontal treatment (Fig. 7). Furthermore, the total OHRQL score showed an improvement at 3 months postoperatively, with this trend continuing steadily until 1 year postoperatively. Regenerative therapy using the combination of rhFGF-2 and DBBM brought about a change in OHRQL as time progressed.

In summary, regenerative therapy using rhFGF-2 in combination with DBBM yielded clinically favorable outcomes as assessed mainly by PPD and CAL. Improvements were also noted in RBF. The improvement in clinical parameters in these patients seems to be in line with the improvement observed in the OHRQL score.

Fig. 5 Surgical procedure and outcomes in Case 3.
(a) Preoperative clinical view (buccal). (b) Intraoperative view. Defect depth 4 mm, width 3 mm. (c) Filling of defect with rhFGF-2. (d) Filled with rhFGF-2 formulation as well as DBBM. (e) Suturing.
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