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Recombinant human platelet-derived growth factor-BB–mediated reconstructive therapy of advanced peri-implantitis bone defects: A case series

KEY WORDS
growth factors, guided bone regeneration, peri-implantitis

ABSTRACT

Background: The treatment of advanced peri-implantitis–related bone defects is often associated with ineffective efforts to halt disease progression. The objective of this case series was to evaluate the performance of reconstructive therapy for the management of advanced peri-implantitis using recombinant human platelet-derived growth factor-BB as an adjunctive biological agent.

Materials and methods: A prospective case series study on advanced intrabony peri-implantitis bone defects (≥ 50% bone loss) was performed. Clinical and radiographic variables were collected at baseline (after non-surgical therapy) and 12 months after surgical treatment. Implant surface decontamination of the intrabony component was carried out using titanium brushes and the electrolytic method. Before grafting, recombinant human platelet-derived growth factor-BB was applied on the implant surface. A mixture of mineralised allograft and xenograft hydrated with recombinant human platelet-derived growth factor-BB and covered by a collagen barrier membrane was used for reconstructive therapy. Disease resolution was defined as an absence of bleeding on probing, pocket depth < 6 mm and no radiographic evidence of progressive bone loss. Descriptive statistics were performed to assess the effect of treatment on the clinical and radiographic variables.

Results: A total of 10 patients exhibiting 13 advanced peri-implantitis-related bone defects were included. Implant survival at the 1-year follow-up was 100%. No major complications occurred during the early healing phase. All the clinical parameters, with the exception of keratinised mucosa, and radiographic parameters yielded statistical significance. In particular, mean pocket depth decreased by 4.5 mm and the mean Sulcus Bleeding Index was reduced by 1.8. Radiographic intrabony defects displayed a significantly narrower, shallower and less angled configuration at the 1-year follow-up. The disease resolution rate at implant level was 61.5%.

Conclusion: The surgical reconstructive strategy involving the use of recombinant human platelet-derived growth factor-BB proved to be safe and effective for treating advanced peri-implantitis–related bone defects.

Conflict-of-interest statement: *AM receives fees for lecturing and participating in other education-related events from Straumann (Basel, Switzerland) and SigmaGraft (Fullerton, CA, USA). MHAS was a scientific consultant for Lynch Biologics (Franklin, TN, USA) at the time of inception of this study. The other authors declare no conflicts of interest relating to this study.*

Introduction

The predictability and effectiveness of the different therapeutic modalities to treat peri-implantitis have been subject to debate.[1] In fact, multiple reports have demonstrated that the achievement of peri-implant health following peri-implantitis treatment is dependent on multiple factors.[2-4] Examples of this include patients who fail to comply with supportive peri-implant care, smokers and patients with advanced forms of periodontitis, all of whom are more prone to disease recurrence.[2,3] Other local factors that lead to a tendency for peri-implantitis treatment to fail include implants lacking or having only a narrow band of keratinised mucosa (KM) on the buccal aspect, posterior implants and those where suppuration was observed at baseline.[5-7] In particular, defect configuration and defect angle seem to have an impact on the reconstructive outcome.[8,9] Nevertheless, one of the strongest indicators of failure is the magnitude of bone loss (i.e., disease severity) related to peri-implantitis.[10] de Waal et al[4] demonstrated that bone defects extending ≥ 5 to 7 mm are significantly less likely to result in favourable outcomes when compared to milder forms of peri-implantitis. Ravida et al[11] showed that the chances of disease recurrence after surgical treatment are 15 and 20 times higher for implants displaying ≥ 25% to 50% and ≥ 50% bone loss, respectively, when compared to peri-implantitis bone defects extending < 25% of the implant length. Other patient-related (i.e., plaque control or deleterious habits)[6] and site-related factors (i.e., implant position or soft tissue characteristics)[5,12] have also demonstrated an association with disease recurrence.

Biologics are a group of mediators that exert an effect that ultimately aims to promote tissue regeneration and reduce the level of local inflammation.[13,14] They help to advance a wide variety of cellular events in wound healing, including DNA synthesis, chemotaxis, cell differentiation, mitogenesis and matrix biosynthesis.[15] In particular, recombinant human platelet-derived growth factor-BB (rhPDGF-BB) has been found to be a potent mitogenic agent. It is naturally released by blood platelets after binding to specific cell surface receptors and may promote osteoblast migration and proliferation.[16] Recently, the American Academy of Periodontology Best Evidence Consensus explored the use of rhPDGF-BB on alveolar ridge preservation/reconstruction and implant site development.[13] This group reported that rhPDGF-BB combined with a bone graft material may outperform other treatment methods as measured by histomorphometry and accelerate the wound healing process.[17]

Other biologics, such as enamel matrix derivatives and autologous platelet derivatives, have been tested in the treatment of peri-implant diseases.[18,19] Froum et al[20] reported 168 cases of peri-implantitis in 100 patients treated with reconstructive therapy using enamel matrix derivative or rhPDGF-BB combined with mineralised freeze-dried bone and/or bovine bone and a barrier membrane. Over a mean study period of 3.6 years, probing pocket depth (PPD) was reduced by 5.1 mm and bleeding on probing (BOP) was eliminated in 91% of the treated implants.[20] In light of the promising outcomes demonstrated, the objective of the present case series was to evaluate the clinical and radiographic performance of reconstructive therapy for the management of peri-implantitis using rhPDGF-BB as an adjunct to implant surface decontamination and as a biological additive to a composite bone replacement graft.

Materials and methods

The present prospective case series was conducted from September 2022 to March 2024 in accordance with the Declaration of Helsinki on human studies, following approval from the Ethics Committee of the University of Extremadura, Badajoz, Spain. Patients were recruited at the CICOM-MONJE Institute, Badajoz, Spain. Patients signed a written informed consent, and their data were kept anonymised. The study was registered and approved at www.clinicaltrials.gov (NCT06390124) and reported according to the Preferred Reporting Of CasE Series in Surgery (PROCESS) 2020 guidelines.

Study sample

Consecutive patients exhibiting advanced peri-implantitis–related bone lesions[21] were recruited and

assessed from September 2022 to March 2024. Moreover, these patients needed to display pure intrabony or combined defects (intrabony and supracrestal component and/or outside of the bony housing) exhibiting ≥ 3 mm depth, whether crater-like or circumferential. The inclusion criteria were as follows:

- aged between 18 and 80 years;
- non-smokers;
- no presence of infectious disease at the time of implant placement or during the maintenance programme;
- no presence of systemic disease;
- no medication known to alter bone metabolism;
- either partially or completely edentulous patients with no active periodontal disease.

Peri-implantitis was defined according to the 2017 World Workshop of Periodontal and Peri-implant diseases (probing depth ≥ 6 mm, bone level ≥ 3 mm apical of the most coronal portion of the intrabony part of the implant based on periapical radiographs).[22] Moreover, only peri-implantitis–related advanced bone defects (≥ 50% bone loss) were included.

Outcomes

The primary outcome was disease resolution, whereas the secondary outcome was changes in the clinical and radiographic parameters from baseline to the final examination.

Primary outcome

Disease resolution was evaluated at the 12-month follow-up. Peri-implantitis was considered "resolved" if the following criteria were met:

- lack of bleeding and/or suppuration on gentle probing (~0.2 N)
- PPD ≤ 5 mm;
- no progressive radiographic bone loss within the standard error (SE ≥ 1 mm).[23]

Clinical assessment

Clinical parameters and indices were recorded at baseline (5 to 6 weeks after non-surgical therapy) and 12 months after surgery by one previously calibrated (intraoperative k-value > 85% based on a previous examination of 15% of the overall sample, i.e., two patients) examiner (AM). They included PPD,[24] modified Sulcus Bleeding Index (mSBI),[25] mucosal recession (MR), keratinised mucosa (KM), suppuration grading index (SGI)[26] and the intraoperative intrabony component (IC).[8] All clinical measurements except for KM were recorded at six sites.

Radiographic assessment

At baseline, defects were assessed according to the classification proposed by Monje et al[27] on bone morphology. Moreover, periapical radiographs were taken by applying a long cone paralleling technique assisted by the intraoral radiographic positioning system. Marginal bone level (MBL), defect width (DW) and intrabony defect angle (DA)[8] were recorded at baseline and at 12 months and were determined by a blinded examiner (RP) who calibrated the radiographs based on the known thread distance and reached an intraoperative k-value ≥ 0.8 on a representative sample before starting the study.

Peri-implantitis treatment

Oral hygiene instructions were provided as part of the diagnostic phase. All eligible patients underwent non-surgical therapy, as described elsewhere,[28] at least 5 to 6 weeks prior to the surgical reconstructive phase performed by one operator (AM), as published elsewhere.[5] Prostheses were removed prior to surgical treatment to improve access. Patients displaying persistent clinical signs of inflammation (≥ 6 mm PPD with bleeding and/or suppuration on probing) were encouraged to undergo surgical reconstructive therapy. At this stage, following the administration of local anaesthesia, a marginal internal bevel incision was made to raise a full-thickness flap. Debridement of granulation tissue was performed using curettes. Supracrestal components and/or areas outside of the reparative potential were managed through implantoplasty using a tungsten carbide bur (Hager & Meisinger, Neuss, Germany) to make the implant surface smoother and increase the

adaptation/homeostasis of fibroblasts in the supracrestal component.[29] Surface decontamination of the intrabony component was performed using NiTi brushes (Hans Korea, Gyenonggi-do, South Korea) for approximately 2 to 3 minutes at 600 rpm. Subsequently, GalvoSurge (Straumann, Basel, Switzerland) was employed for 2 minutes for further decontamination followed by saline irrigation. This was followed by the application of GEM 21S (Lynch Biologics, Franklin, TN, USA) to the implant surface. The reconstructive therapy involved a composite graft of mineralised freeze-dried bone (Lynch Biologics) mixed with xenograft (InterOss SigmaGraft, Fullerton, CA, USA) in a ratio of 1:1 that was hydrated by GEM 21S. A collagen barrier membrane (Lynch Biologics) was placed over the graft to facilitate its containment and help guide the healing process. Nylon 5.0 sutures were employed with an interrupted technique. All sites underwent transmucosal (non-submerged) healing.

Patients were instructed to apply chlorhexidine and chitosan gel three times a day in the area for the first 2 weeks and to take 750 mg systemic amoxicillin (two tablets daily) for 7 days. Postsurgical inflammation was controlled by 600 mg ibuprofen (one tablet every 5 to 6 hours for the first 5 days). Prostheses were placed approximately 3 weeks after reconstructive therapy, then self-performed interproximal oral hygiene devices were tailored according to the embrasure width. All the patients enrolled in the present study subsequently adhered to a 3- to 4-month recall schedule of supportive peri-implant maintenance therapy, as described elsewhere.[28] Postoperative complications that occurred during the follow-up period were documented.

Statistical analysis

Descriptive analysis was performed to evaluate the clinical and radiographic parameters at every time point, as well as to assess changes from baseline (prior to treatment) to the 1-year follow-up. To assess statistical significance in the outcomes, a Friedman test and a Wilcoxon signed-rank test were used, with an assumed *P* value threshold of 0.05 for significance.

Results

Demographics

A total of 10 patients (eight women and two men) with 13 advanced peri-implantitis–related bone defects were included. Patients' mean age was 59.20 ± 9.11 years. Mandibular implants represented 53.8% of the overall sample size, and posterior implants constituted 76.9% of the treated cohort. Combined defect morphology (class 3B) was the most prevalent (53.8%). Mean intraoperative defect depth was 4.84 ± 1.42 mm, whereas the mean deepest intraoperative defect depth was 5.07 ± 1.55 mm. Mean MBL at baseline was 5.67 ± 1.31 mm, and the mean deepest MBL was 6.13 ± 1.36 mm. Additionally, the mean PPD at baseline was 7.48 ± 1.85 mm, and the mean deepest PPD was 9.38 ± 1.80 mm.

All the implants survived over the follow-up period to give an implant survival rate of 100%. Two patients agreed to have their prostheses modified or changed due to the inadequate access for oral hygiene observed at baseline. Three patients and six implants reported wound dehiscence at the 3-week follow-up that was treated accordingly through professionally and self-administered local application of chlorhexidine gel. At the 3-month follow-up (upon first appointment for supportive care after surgical therapy), all patients were found to have undergone uneventful healing. No complications were reported thereafter.

Clinical outcomes

Table 1 presents the clinical variables at baseline and the outcomes at the 1-year follow-up. All variables except for KM exhibited robust statistically significant changes, with mean PPD and mSBI displaying the most significant changes (Fig 1); mean PPD decreased by 4.50 ± 1.64 mm ($P < 0.001$) and mean mSBI was reduced by 1.88 ± 0.82 ($P < 0.001$). In addition, when comparing the deepest sites from baseline to 1 year after treatment, mean PPD was 3.38 ± 0.76 mm with a statistically significant change of 6.00 ± 1.52 mm ($P < 0.001$). It is important to note that mean KM decreased by 1.00 ± 1.77 mm and that mean MR increased by 2.46 ± 2.43 mm but with a high degree of variability, as noted by the standard deviation.

Table 1 The investigated variables at baseline and at the follow-up examination, as well as the change and corresponding *P* value

Outcome variable	Baseline	Follow-up	Change, *P* value
Mean PPD, mm	7.48 ± 1.85	2.98 ± 0.64	4.5 ± 1.64, < 0.001
Deepest PPD, mm	9.38 ± 1.80	3.38 ± 0.76	6 ± 1.52, < 0.001
Mean mSBI	2.03 ± 0.94	0.15 ± 0.28	1.88 ± 0.82, < 0.001
Mean SGI	0.23 ± 0.28	0.01 ± 0.04	0.32 ± 0.27, 0.01
Mean KM, mm	3.84 ± 1.77	2.84 ± 1.77	−1 ± 1.77, 0.06
Mean MR, mm	0.84 ± 1.72	−1.61 ± 1.66	−2.46 ± 2.43, < 0.01
Mean radiographic MBL, mm	5.67 ± 1.31	4.07 ± 0.94	1.59 ± 1.12, < 0.001
Deepest radiographic MBL, mm	6.13 ± 1.36	4.39 ± 0.95	1.74 ± 1.25, < 0.001
Mean radiographic DW, mm	2.94 ± 0.84	2.45 ± 0.78	0.48 ± 0.81, 0.04
Mean radiographic DA, degrees	49. 85 ± 15.78	59.61 ± 8.72	9.75 ± 11.31, < 0.001

Radiographic outcome

Statistical significance was reached for all the radiographic variables explored (Table 1). Mean MBL decreased by 1.59 ± 1.12 mm ($P < 0.001$). The deepest MBL measurement at 1 year was 4.39 ± 0.95 mm compared to the baseline measurement of 6.13 ± 1.36 mm, with a statistically significant change of 1.74 ± 1.25 mm ($P < 0.001$); this represented radiographic bony fill of ~30%. DW tended to become narrower ($P < 0.04$), but mean DA increased by 9.75 ± 11.31 degrees ($P < 0.001$).

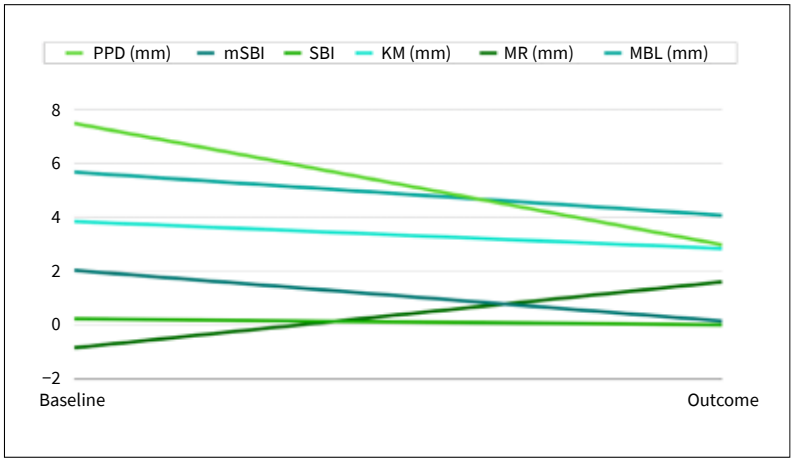

Fig 1 Evolution from baseline to outcome at the 1-year follow-up for the clinical and radiographic (MBL) variables.

Disease resolution

In the implant level analysis, disease resolution was observed in 61.53% of cases. It is worth noting that at the 1-year follow-up, PPD was ≤ 4 mm in all sites. Disease progression/recurrence was predominantly attributable to the presence of BOP at the final evaluation, which was found to be profuse (mSBI ≥ 2) in only three cases (23.07%). Accordingly, disease resolution was 76.93% if defined as ≤ 1 site as recently suggested by the Implant Dentistry Core Outcome Set and Measurement (ID-COSM).[30]

Discussion

The morphology of advanced peri-implantitis–related bone defects have been suggested to be an indicator for the potential failure to halt disease progression.[11] The challenge involved in the effective management of advanced peri-implantitis lesions may reside in the inconsistent ability to perform total surface decontamination due to the difficulty in reaching the apical portion of the contaminated implant surface. Moreover, lesion morphology may limit regenerative efforts to reestablish a MBL that reduces the post-treatment sulcus to a threshold compatible with maintaining peri-implant health (≤ 5 mm). To overcome these shortcomings, it was hypothesised that the use of rhPDGF-BB may enhance the effectiveness of achieving disease resolution in advanced peri-implantitis cases. Interestingly, this case series demonstrated that all the clinical and radiographic variables except for KM experienced a statistically significant change. Moreover, disease resolution at the 1-year follow-up

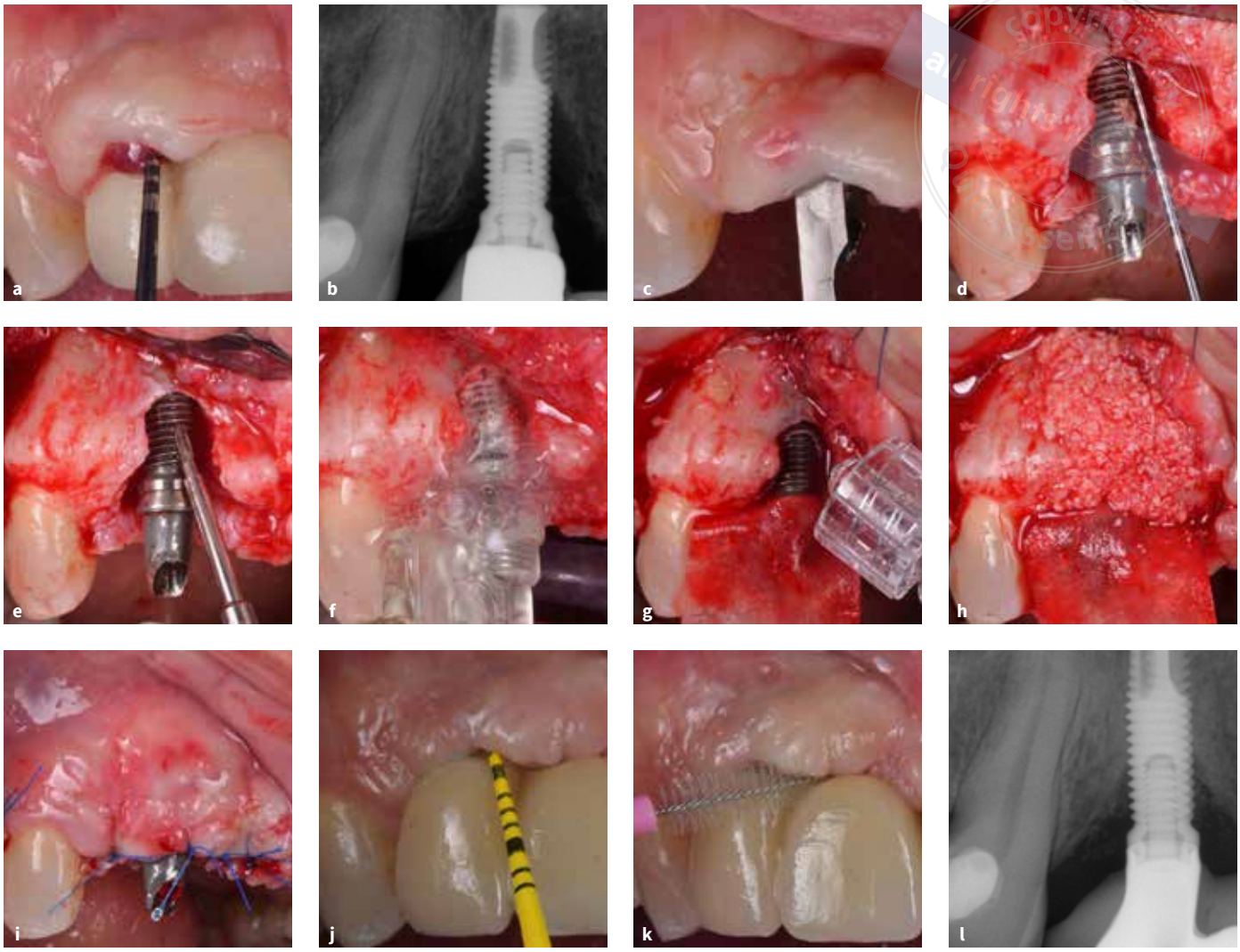

Fig 2a to l Advanced crater-like peri-implantitis–related defect managed with reconstructive therapy, applying rhPDGF-BB to the implant surface and soaking in the bone grafting material. Baseline evaluation **(a)**, baseline periapical radiograph **(b)**, internal bevel marginal incision to gain access **(c)**, intra-operative defect severity **(d)**, mechanical decontamination using NiTi brushes **(e)**, electrolytic decontamination using GalvoSurge **(f)**, application of GEM 21S on the implant surface **(g)**, a mixture of xenogeneic and allogeneic grafts was used as a grafting material and a collagen membrane as a barrier **(h)**, transmucosal healing was promoted **(i)**, clinical evaluation at the 1-year follow-up **(j)**, interproximal access was favoured to facilitate self-performed oral hygiene measures **(k)**, periapical outcome at the 1-year follow-up **(l)**.

amounted to 61.5%. In this sense, PPD was ≤ 4 mm across the test sample. These outcomes therefore support the safety and effectiveness of rhPDGF-BB in complex peri-implantitis–related bone defects (Fig 2 to 4). Nevertheless, it is advisable to interpret these findings with caution given the nature and design of the study and the numerous technical aspects involved in the management of peri-implantitis.

The use of biological agents in the management of peri-implantitis has been seldom explored. In a randomised clinical trial (RCT), Hamzacebi et al[31] compared open flap debridement (OFD) to OFD combined with platelet-rich fibrin (PRF) as a reconstructive agent. At the 6-month follow-up, PPD reduction (mean difference approximately 0.4 mm), attachment gain (mean difference approximately 1.5 mm) and keratinised mucosa gain favoured the sites where PRF was used. Isler et al[31] evaluated the performance of concentrated growth factors (CGFs) in combination with barrier membrane–mediated reconstructive therapy. At 36 months, the

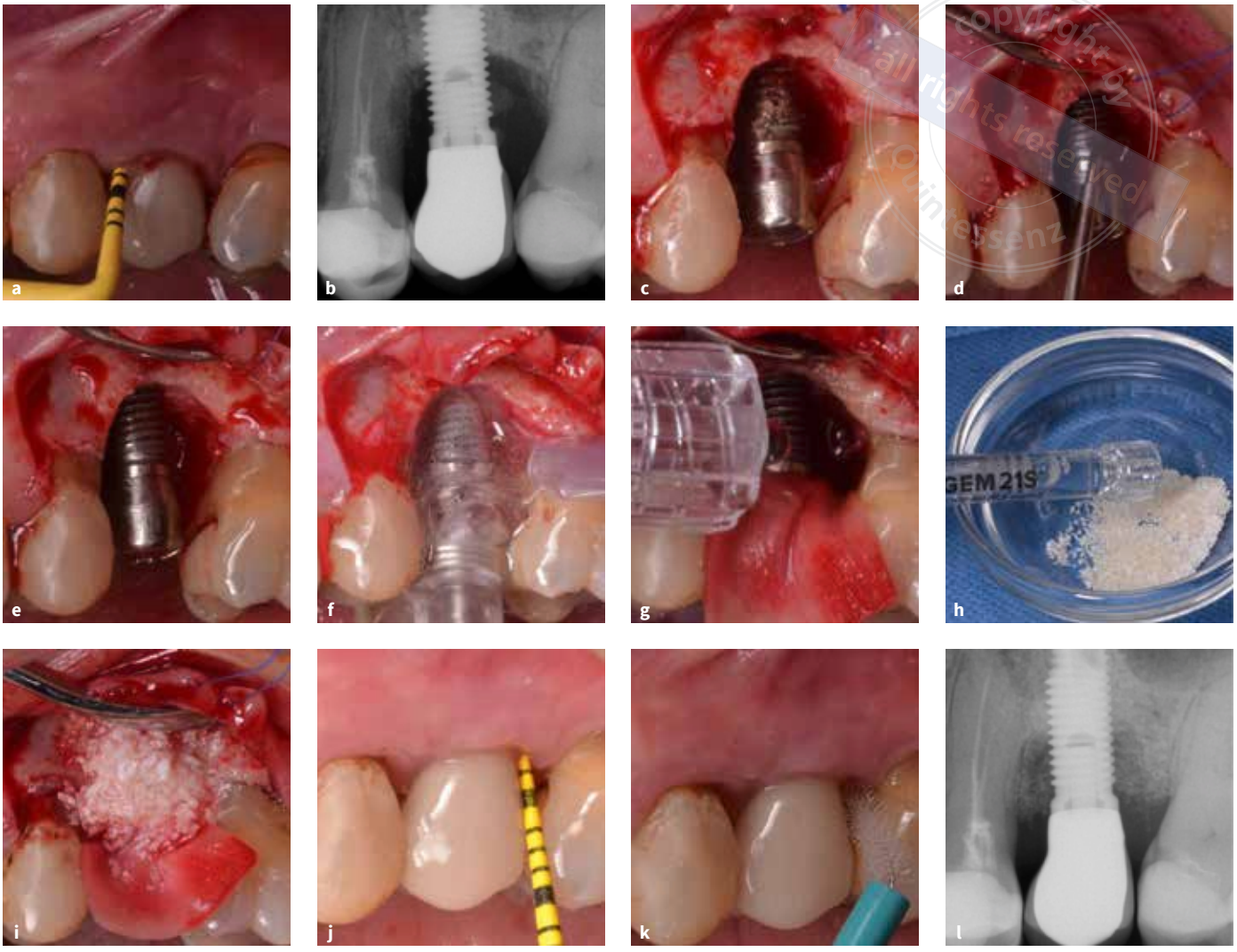

Fig 3a to l Advanced crater-like peri-implantitis–related defect managed with reconstructive therapy, applying rhPDGF-BB to the implant surface and soaking in the bone grafting material. Baseline evaluation **(a)**, baseline periapical radiograph **(b)**, contaminated surface **(c)**, mechanical decontamination using NiTi brushes **(d)**, implant surface after biofilm and calculus removal **(e)**, electrolytic decontamination using GalvoSurge **(f)**, application of GEM 21S on the implant surface **(g)**, biomaterials were soaked with GEM 21S prior to grafting **(h)**, a mixture of xenogeneic and allogeneic grafts was used as a grafting material with a collagen membrane **(i)**, clinical evaluation at the 1-year follow-up **(j)**, interproximal access was favoured to facilitate self-performed oral hygiene measures **(k)**, periapical outcome at the 1-year follow-up **(l)**.

use of collagen membrane resulted in greater PPD reduction compared to the employment of CGF.[31] Conversely, at 60 months, Isehed et al[32] showed that radiographic bone level was superior in sites managed with enamel matrix derivatives (EMDs)–mediated reconstructive therapy (mean difference approximately 1 mm) compared to control sites. Nevertheless, no significant differences were noted in the evaluated clinical parameters. The use of EMD combined with barrier membrane resulted in favourable clinical outcomes at 1 year in a case series by Pilenza et al.[33] In this study, the authors demonstrated a mean decrease in PPD of 2.2 mm, a 70% reduction in BOP-positive sites and an increase in MBL of 1.1 mm.[33] Similarly, Froum et al[20] treated by means EMD- and rhPDGF-BB–mediated reconstructive therapy combined with mineralized freeze-dried bone and/or bovine bone and a barrier membrane. At a mean follow-up period of 3.6 years, PPD was reduced by 5.1 mm and BOP was eliminated in 91% of the treated implants.[20] The outcomes of the present study provide evidence of the potential

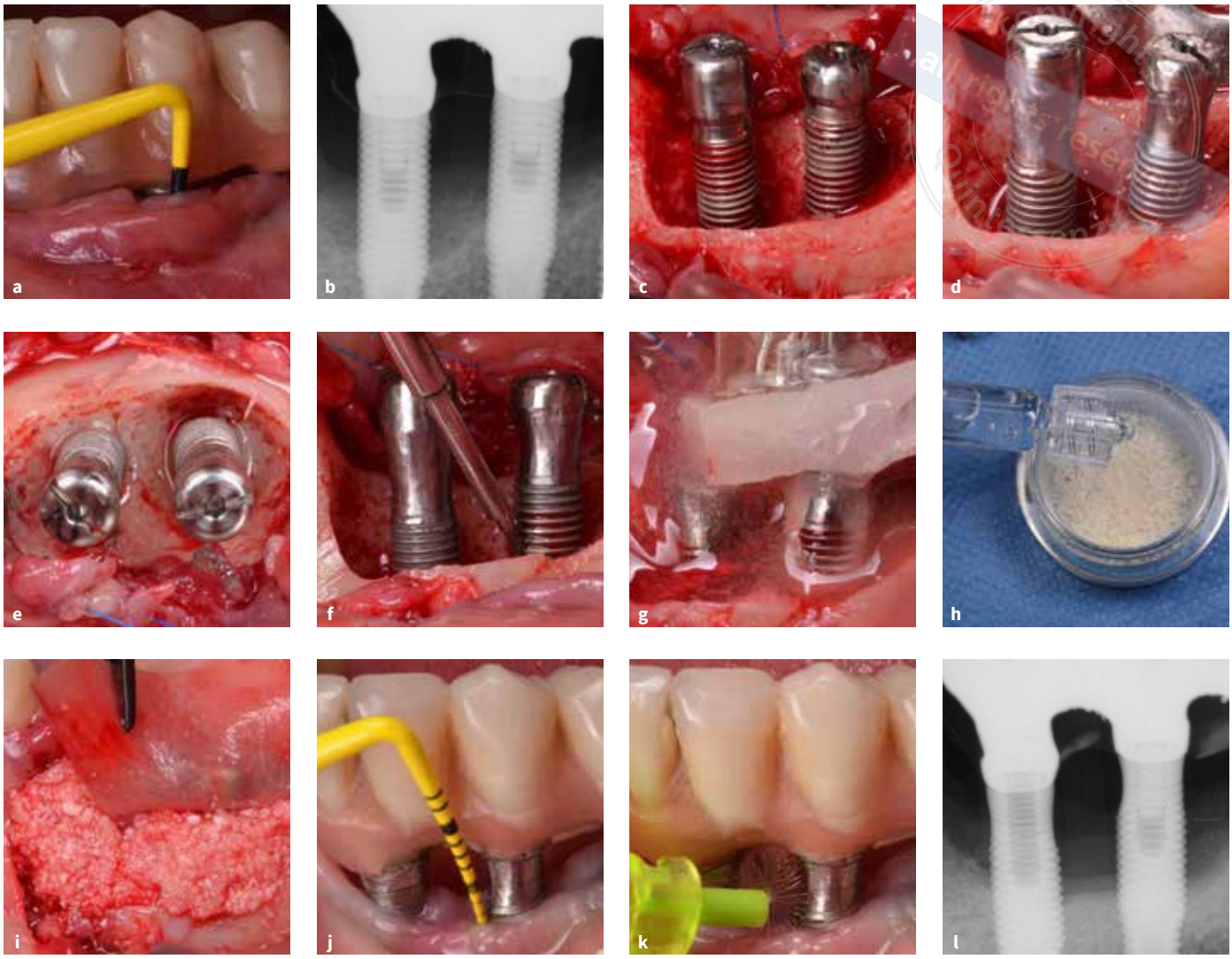

Fig 4a to l Advanced combined peri-implantitis–related bone defect managed with reconstructive therapy, applying rhPDGF-BB to the implant surface and soaking in the bone grafting material and performing implantoplasty in the supracrestal component. Baseline evaluation **(a)**, baseline periapical radiograph **(b)**, contaminated surface **(c)**, frontal view of implantoplasty performed at the supracrestal component **(d)**, occlusal view immediately after implantoplasty **(e)**, implant surface decontamination of the intrabony compartment **(f)**, electrolytic decontamination using GalvoSurge **(g)**, application of GEM 21S on the bone graft **(h)**, a mixture of xenogeneic and allogeneic grafts was used as a grafting material with a collagen membrane **(i)**, clinical evaluation at the 1-year follow-up **(j)**, interproximal access was favoured to facilitate self-performed oral hygiene measures **(k)**, periapical outcome at the 1-year follow-up **(l)**. Note the flattening of the alveolar bone architecture.

role that rhPDGF-BB may play in treating advanced bone defects. In fact, the mean PPD reduction was 4.5 mm, with many of the lesions having some non-contained components. It is important to note that a mixture of xenogeneic and allogeneic bone grafts was used as a carrier. This composite mixture was selected for several reasons. The allograft enabled incorporation of the growth factor, and studies also suggest that allografts may be more biologically compatible in humans to encourage cell adhesion[34] while allowing slow release of the agent so the allograft could soak the agent to promote slow release, whereas the xenograft will act as a longer-term scaffold for cell migration. However, Nevins et al[35] demonstrated through human histology that by adding rhPDGF-BB to particulate anorganic bovine bone, it was possible to increase the rate of replacement of this normally slowly resorbing material with newly formed bone. Histologically, they observed large areas of dense, well-formed lamellar bone

throughout the intact core specimens in more than half of the grafted sites.[35] The other benefit to adding rhPDGF-BB to the graft materials and to the implant surface is its ability to help increase blood supply, which could aid in the healing of more challenging osseous defects.[36] Moreover, rhPDGF-BB, unlike other growth factors, has a hydrophilic carrier vehicle that will enhance the likelihood of surface wettability to allow for reosseointegration and provides a consistent and quantifiable amount of growth factor, which sets it apart from those procured from the patient's own blood.

Surface decontamination plays a critical role in the successful reconstructive treatment of peri-implantitis.[37] If an implant surface free of plaque and calculus, endotoxins and organic debris is not achieved, it may not be possible to promote peri-implant bone formation, which would reduce the likelihood of reducing PPD. Moreover, contemporary implants have grooves and porosities that make this a challenging task.[37] Mechanical, chemical and pharmacological agents have been explored in vivo and in vitro, proving their relative effectiveness in eliminating endotoxins, destroying the organic components and reducing bacterial concentrations[37]; however, none of these approaches have consistently demonstrated superiority in a clinical setting.[38] Nevertheless, it is advisable to use mechanical methods, such as titanium brushes, to eliminate the superficial biofilm and calculus. This is followed by the application of chemical agents, such as hydrogen peroxide, that may contribute to diluting bacterial concentrations and eliminating endotoxins, thus favouring subsequent osteoblastic cell proliferation[39,40]; however, the predictability of these strategies is limited by defect depth and configuration. Thus, no gold standard method for surface decontamination is known as yet. Recently, the electrolytic method (GalvoSurge) was shown to achieve near-complete eradication of contaminants on the implant surface without causing any surface damage, while improving hydrophilicity and promoting the early osteogenic response of bone marrow mesenchymal stem cells.[41] In the clinical setting, the use of GalvoSurge yielded significantly more radiographic bone fill and improvements in clinical parameters compared with baseline data.[42] Single-centre outcomes from a multicentre RCT demonstrated a disease resolution rate of 91% when using this strategy combined with mechanical methods.[28] The mean difference with the control group (hydrogen peroxide and titanium brushes) was 16%.[28] The difference in disease resolution rate achieved in the abovementioned RCT and in the present case series can be attributed to the differences in baseline defect depth. In fact, the uniqueness of the present consecutive case series is that all the peri-implantitis cases included were advanced in severity. Hence, it strongly suggests the potential to halt disease progression in such scenarios.

Caution must be exercised when interpreting the present findings due to the limited sample size. The fact that a personalised occlusal registration key was not used (a positioning system to maximise the reliability of the radiographs was employed instead) and that all the interventions were performed by a single operator with experience in the management of peri-implantitis should also be considered when interpreting the results. Nevertheless, the authors deem this report timely due to the limited data available on the use of biological agents to manage peri-implantitis. Thus, it is advisable to seek to gain further insight into the use of rhPDGF-BB in a larger number of patients with a wider group of clinicians and to test its efficacy and effectiveness when compared to other reconstructive strategies through RCTs.

Conclusions

The surgical reconstructive strategy described involving rhPDGF-BB proved to be safe and effective for treating advanced peri-implantitis–related bone defects.

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