A Combined Treatment for a Case of Peri-Implant Bisphosphonate-Related Osteonecrosis of the Jaw

Nicola Alberto Valente[1] and Sebastiano Andreana[2]

[1]Department of Periodontics and Endodontics; [2]Department of Restorative Dentistry, State University of New York at Buffalo, School of Dental Medicine, Buffalo, NY, USA

Abstract

Objective: Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is rarely reported as a complication after implants placement. In this article we report a combined treatment for a rare case of peri-implant BRONJ.

Methods: A 71-year-old female patient presented for follow-up of a 4.3 x 13 mm implant placed on first upper-left premolar position 3 years prior. She was complaining of soreness of the area and bleeding when brushing. The patient had a history of breast cancer (removed 7 years prior) for which she was taking anastrozole 1mg/day, causing a decrease in mineral bone density as side effect, for which she was prescribed a side-therapy of oral risedronate 35 mg/week taken for 4 years and stopped 2 years prior. A 9 mm deep pocket was detected on the mesial-buccal aspect of the implant. At the first visit local minocycline microspheres delivery was performed as antibacterial and anti-inflammatory agent. The patient was seen 10 weeks later with the presence of a bone sequestrum on the mesial-palatal aspect of the implant. A surgical minimally invasive single-flap approach was done to minimize periosteal elevation. Decontamination with EDTA-gel followed by delivery of rh-PDGF (recombinant platelet derived growth factor) with β-TCP (β-tricalcium phosphate) stabilized with a $CaSO_4$ barrier. A cycle of four consecutive 810 nm diode-laser-biostimulation visits was performed to promote fibroblasts growth. An 18-month post-surgical follow-up showed 3 mm residual probing depth (PD) and an absence of gingival inflammation with no symptoms reported by the patient.

Results: Antimicrobial, regenerative and biostimulation therapies were implemented to successfully treat BRONJ around an osseointegrated implant. The results showed noticeable PD reduction and radiographic bone regeneration after 18 months.

Conclusions: A combined therapy aiming at regeneration of bone and soft tissues around osseointegrated implants was successful for treatment of implant-associated BRONJ.

Key words: Guided tissue regeneration, platelet-derived growth factor, osteonecrosis, bisphosphonates

Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ), described for the first time in literature by Marx (Marx, 2003), is a condition characterized by the exposure of the maxillary or mandibular bone that persists for more than 8 weeks in a patient with a history of intake of medications from the class of bisphosphonates and who has not previously been subjected to radiation therapy of the jaw bones (Marx *et al.*, 2005).

It clinically appears as an exposure of the alveolar bone spontaneously, or, more often, it becomes evident after an invasive surgical procedure such as an extraction or, sometimes, the positioning of an implant (Marx *et al.*, 2005).

Bisphosphonates are anti-resorptive medications commonly used, orally, in the treatment of osteoporosis or, intravenously, in oncology to inhibit bone resorption related to malignant neoplastic formations in patients with various malignancies. In addition, several other applications are reported. These drugs are completely resistant to hydrolytic cleavage and accumulate over time in the bone tissue; thus, they have, as a consequence, very long half-lives.

Correspondence to: Nicola Alberto Valente, State University of New York at Buffalo, School of Dental Medicine, Department of Periodontics and Endodontics, 3435 Main Street, Buffalo, NY, 14214 USA. Telephone: +39 3385932069. E-mail: nicolaal@buffalo.edu

Most bisphosphonates have, in fact, half-lives greater than 10 years, and thus are able to exercise their side effects for a long time after cessation of dosing (Glowacki, 2005).

Recently, the American Association of Oral and Maxillofacial Surgeon (AAOMS) has published a position paper focused on this topic, with the purpose of providing risk estimate, risk/benefit comparison, and a clinical guide for differential diagnosis, prevention, and management (Ruggiero *et al.*, 2014). In this document, the special committee of the AAOMS recommends a change in the terminology from BRONJ to medication-related osteonecrosis of the jaw (MRONJ), justified by the necessity to accommodate the growing number of osteonecrosis of the jaw cases associated with other non-bisphosphonate anti-resorptive agents, such as RANK ligand inhibitors (denosumab) and antiangiogenic medications (sunitinib, sorafenib, bevacizumab, sirolimus).

A recent systematic review by the International Task Force on Osteonecrosis of the Jaw states that the management of BRONJ should be based on the stage of the disease, size of the lesions, and the presence of contributing drug therapy and comorbidity (Khan *et al.*, 2015). When conservative therapy is indicated, it should include topical antibiotic oral rinses and systemic antibiotic therapy, and, although it may not necessarily lead to complete resolution of lesions, it may symptomatically provide long-term relief, while localized surgical debridement is indicated in advanced nonresponsive diseases and has usually been shown to be successful. The same review provides evidence of enhanced osseous wound healing with the use of teriparatide and also evaluates experimental therapies including bone marrow stem cell intra-lesional transplantation, low-level laser therapy, local platelet-derived growth factor application, hyperbaric oxygen, and tissue grafting.

Three recent reviews of the literature about the influence of bisphosphonate therapy on implant placement report positive rate and safety results. One of these reviews points to the fact that the studies currently available include moderate to weak evidence, with inherent bias and limitations. It thus implies that the results of the review must be interpreted in its context (Madrid *et al.*, 2009; Javed *et al.*, 2010; Chadha *et al.*, 2013).

In a retrospective study using data from a large cohort of patients with known oral bisphosphonate exposure, subject testimonies (self-reported information pertaining to implant placement and related complications) were confirmed subsequently by dental chart review (Martin *et al.*, 2010). With only 16 patients out of 589, reporting failure of 26 implants, the authors concluded that the influence of bisphosphonates on implants survival should be further investigated. In a subsequent retrospective radiographic study, out of the 362 patients who received implants, 26 subjects, for a total of 51 implants, had a history of bisphosphonates intake, with only 3 implant failures, yielding an implant-based success rate of 94.11% and a subject-based success rate of 88.46% (Zahid *et al.*, 2011). In this latter study, analysis using the GEE statistical method found a statistically significant association between the use of bisphosphonates and implant thread exposure. Thus, the researchers concluded that patients taking bisphosphonates may be at higher risk for implant thread exposure.

In a retrospective multicenter study on 9 patients taking bisphosphonates that developed BRONJ after receiving dental implants, the authors found that the mean interval between the initiation of bisphosphonate treatment and the onset of BRONJ lesions was 60 months, while the mean interval between placement of dental implants and the onset of BRONJ was 34 months (Lopez-Cedrun *et al.*, 2013).

In a different study, 19 patients diagnosed with BRONJ associated with dental implants were analyzed for clinical, radiographic, and histological findings (Kwon *et al.*, 2014). Sixteen patients initiated the bisphosphonate treatment before surgery, and three patients after implant surgery. Nine patients developed the osteonecrotic lesion at an average of 35 months after implant placement and successful osseointegration. The authors were able to identify three bone destruction pattern types: one with complete necrosis of the bone around the implant (frozen type); one with extensive osteolysis around the implant with or without sequestra (osteolytic type); and one showing sequestration of bone with the implant maintaining direct implant-bone contact (en block sequestration type). These authors hypothesize, regarding the "en block" type of peri-implant BRONJ, the possible role of microcracks induced by normal mechanical stress, which needs to be investigated further.

Case presentation

A 71-year-old female Caucasian patient presented for follow-up with a 4.3 x 13 mm implant (Nobel Replace, tapered groovy, Nobel Biocare USA LLC, Yorba Linda, CA, USA) placed in the first maxillary left premolar position 3 years prior. She was complaining of soreness of the area and bleeding when brushing for about two weeks. The patient had a history of breast cancer (removed 7 years prior) for which she was taking anastrozole 1mg/day, causing a decrease in mineral bone density as side effect, for which she was prescribed a side-therapy of oral risedronate 35 mg/week taken for 4 years and stopped 2 years prior. At the time of implant placement, the patient was made aware of the possible risks of undergoing an oral surgery procedure while taking oral bisphosphonates and she signed informed consent. A first episode of bone necrosis with a sequestrum around the implanted area was already reported in the patient's chart at only 6 months after surgery and was removed and cleaned by a previous resident.

At her first appointment with us, a 9 mm deep pocket and bleeding upon probing (BOP) were detected on the mesial buccal aspect of the implant (*Figure 1*). Local minocycline microspheres (Arestin, OraPharma, Inc., Horsham, PA, USA) delivery was performed to have an antibacterial and anti-inflammatory effect. The patient was seen 6 weeks later for follow-up with no changes detected in terms of probing depth (PD) or BOP, and a subgingival irrigation with chlorhexidine gluconate 0.12% was performed. At the next follow-up appointment, 4 weeks later, the presence of a bone sequestrum on the mesial-palatal aspect of the implant was noticed (*Figure 2*). We decided to perform a surgery aimed at removing the necrotic bone in order to regenerate the resulting defect.

Figure 1. During first evaluation a 9 mm pocket associated with bleeding on probing was detected on the mesial-buccal aspect of the implant.

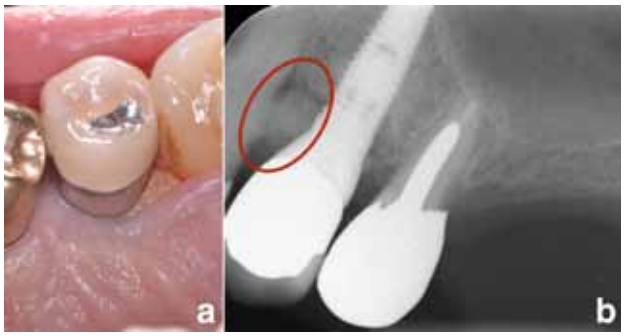

Figure 2. a) A bone sequestrum was visible on the mesial-palatal aspect of the implant ten weeks after the first evaluation, allowing for the diagnosis of bisphosphonates-related osteonecrosis of the jaw. b) Radiographic appearance of the bone sequestrum.

The area was anesthetized via local infiltration of mepivacaine 2% 1:50000, and a surgical minimally invasive single-flap approach was used in order to minimize periosteal elevation and the surgical trauma that could trigger further bone necrosis. The bone sequestrum was carefully removed, ensuring that all the necrotic bone was eliminated from the affected area. The root surface of the adjacent tooth was carefully scaled, and the area was conditioned and decontaminated with EDTA-gel. The area was then grafted delivering rhPDGF-BB (recombinant platelet-derived growth factor-BB) with β-TCP (β-tricalcium phosphate) as carrier (GEM 21S® Growth-factor Enhanced Matrix, Osteohealth® Company, Shirley, NY, USA) and stabilized with a $CaSO_4$ barrier (DentoGen®, Orthogen LLC, Springfield, NJ, USA). The flap was sutured with 4-0 PTFE sutures (Cytoplast™, Osteogenics Biomedical, Inc., Lubbock, TX, USA; *Figure 3*). Systemic antibiotics, amoxicillin 875 mg, were prescribed twice per day for a total of 10 days, starting from the day before the surgery. The patient was instructed to gently dab the surgical area with a local application of chlorhexidine gluconate 0.12% twice per day for 14 days. The suture removal was done 14 days following surgery. A cycle of 4 weekly consecutive biostimulations were performed using a 810 nm diode-laser (2.4G Odyssey, Ivoclar Vivadent Inc., Amherst, NY, USA) set at 0.8 W in continuous pulse energy mode to promote fibroblast growth and enhance the closure of the papilla over the treated area. The fiber optic tip of the laser was kept at 5 mm distance from the surface and moved in an up and down motion for 5 minutes. The laser biostimulation started one week after surgery and was repeated once every 7 days. At the end of the cycle, the soft tissues were completely closed.

During the surgery, a gap was noticed between the margin of the prosthetic crown and the shoulder of the abutment. Thus, a new crown was delivered to ensure a complete seal of the margin.

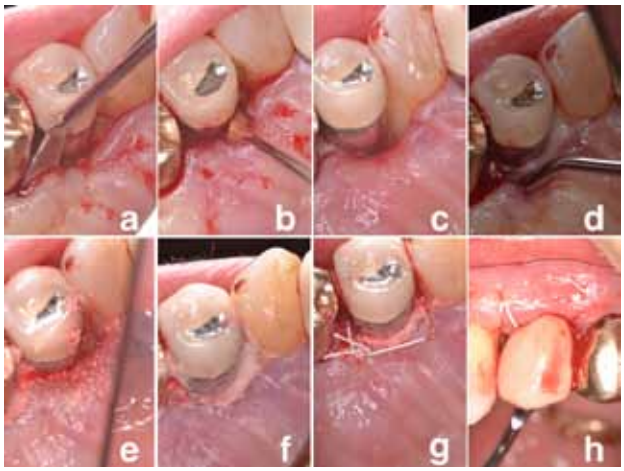

Figure 3. a) Minimal flap reflection only on the palatal side to minimize periosteal elevation. b) Removal of the bone sequestrum from the peri-implant defect. c) The defect was carefully cleaned and the root of the adjacent tooth scaled. d) The area was conditioned with EDTA gel to prepare it to receive the graft and further clean all surfaces. e) rhPDGF was delivered with its carrier β-TCP to elicit bone regeneration. f) The graft was stabilized with calcium sulfate. g) Palatal appearance after suturing with 4-0 ePTFE suture. h) Buccal appearance after suture. A buccal flap was not elevated.

The patient was monitored with recall appointments for 3 months, with good radiographic and clinical results already evident at 9 months (*Figure 4*) that were maintained 2 years after surgery (*Figure 5, Figure 6*). Probing depth values were 4 mm on the mesial-buccal aspect and 3 mm on the mesial-palatal aspect during this time.

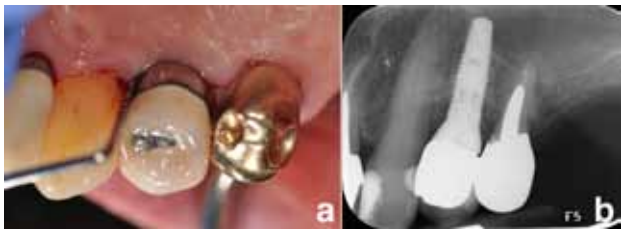

Figure 4. Clinical and radiographic control after 9 months. The probing depth where the sequestrum was found is already reduced to 3 mm. The x-ray shows no evidences of bone necrosis.

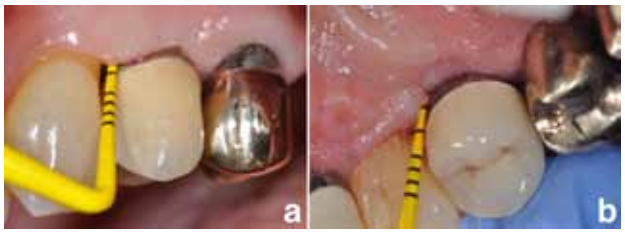

Figure 5. Clinical appearance after 2 years. Both buccal and palatal probing depths are stable within healthy ranges.

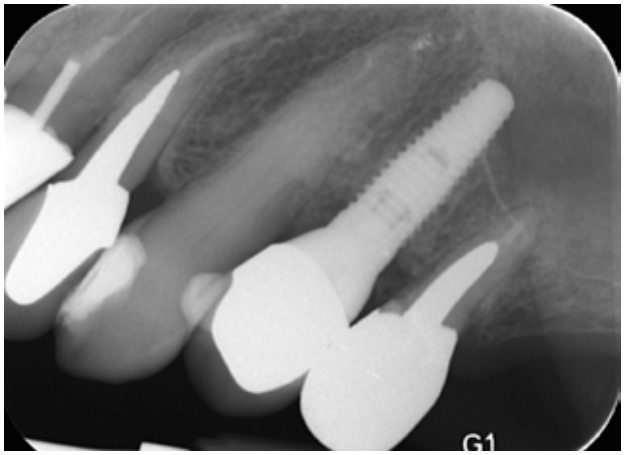

Figure 6. Radiographic appearance after 2 years showing evidence of regeneration and a stable radiographic appearance of the bone.

Discussion

The present case report documented a case of peri-implant BRONJ successfully treated with a minimally invasive surgical approach and regeneration using rhPDGF-BB + β-TCP and $CaSO_4$ barrier. This was followed by laser biostimulation implemented with the aim of improving soft tissue healing over the area.

Although the prevalence of BRONJ is considered to be extremely low for patients receiving oral bisphosphonate, it increases after 4 or more years of exposure, as in the case here reported (Ruggiero *et al.,* 2014).

The rising incidence of BRONJ indicates the importance of communication, not only between the oncologist and the patient, but also between the oncologist and the dentist/oral surgeon. It has been suggested that prior to commencement of therapy, patients have an oral health assessment and be educated about the risks of BRONJ (Al-Zoman *et al.*, 2013).

Non-surgical treatment with delivery of local minocycline, although it has been demonstrated as having encouraging effects in terms of clinical and microbiological parameters when used in cases of implants affected by peri-implantitis, was in this particular case ineffective because the cause of the BOP and deep PD was nonbacterial (Schar *et al.*, 2013; Bassetti *et al.*, 2014; Persson *et al.*, 2006; Salvi *et al.*, 2007). This was revealed by the finding of a bone sequestrum at the time of the third visit.

In February 2009 two different articles were published by two groups of authors who proposed a new minimally invasive surgical technique with flap elevation performed only on one side of the ridge. This was to improve the primary closure and minimize the surgical trauma during periodontal reconstructive surgery (Trombelli *et al.*, 2009; Cortellini *et al.*, 2009). In the case presented here the single flap technique was used to reduce the surgical trauma to the minimum and to prevent the possible triggering of osteonecrosis.

In another case, a minimally invasive approach was used to prevent triggering of osteonecrosis in a patient with 10-year history of bisphosphonate intake. It describes a flapless extraction of a tooth, and the graft of the socket with $CaSO_4$ and a delayed implant placement (Sunkara *et al.*, 2010).

The use of rhPDGF-BB has already been demonstrated as safe and effective in the treatment of periodontal osseous defects (Froum *et al.*, 2015; Nevins *et al.*, 2014; Nevins *et al.*, 2003; Ridgway *et al.*, 2008). It stimulates a significant increase in the rate of CAL gain, reduces gingival recession, and improves bone fill in relation to using β-TCP bone substitute alone (Nevins *et al.*, 2005). The application of rhPDGF-BB in this case follows the findings of two *in vitro* studies conducted in our institution. In the first study, cells from a necrotic alveolar bone in a multiple myeloma patient and non-necrotic cells from a breast cancer patient were exposed to PDGF, with a consequent change in the alkaline phosphatase activity. Both patients were on long-term bisphosphonate treatment. The proliferation and viability was suggestive of normal osteoblastic cell responses that were observed in cultures from a donor of the same gender and age, but not on bisphosphonate treatment. The proliferation, measured with a tritiated thymidine assay,

was significantly increased by PDGF at a concentration that typically produces this effect in cells obtained from noncancer patients not on long-term bisphosphonate therapy, indicating another similarity in responses to bone regulatory agents in cells from bisphosphonate-treated patients (Rao *et al.*, 2009). In a second study, cultures of human alveolar osteoblastic cells were exposed to alendronate, a commonly used bisphosphonate, and it produced a significant decrease in mineralization. In contrast, exposure to PDGF produced a significant increase in mineralization that was not altered when the PDGF was co-incubated with alendronate (Barres *et al.*, 2015).

Laser biostimulation using low-level diode lasers has been proposed, in several studies, as a protocol to improve post-surgical healing and regeneration of both soft and hard tissues, and has already demonstrated being able to enhance the number, proliferation and the migration of fibroblastic cells *in vitro*. Thus, it represents a possible safe and reliable method for promoting and improving soft tissue healing that certainly deserves more thorough clinical investigation (Hakki *et al.*, 2012; Basso *et al.*, 2012; Aoki *et al.*, 2015; Dogan *et al.*, 2014; Sanz-Moliner *et al.*, 2013).

To our knowledge, the case described here is the only successfully treated case with regeneration of lost bone; other case reports of BRONJ occurring around osseointegrated implants describe treatments involving the removal and replacement of the fixtures (Petropoulos *et al.*, 2014; Lopez-Cedrun *et al.*, 2013). The regeneration and preservation of the implant was possible because the osteonecrosis did not involve the whole alveolar bone surrounding the implant, but only a limited area. According to Kwon *et al.* (2014), the classification of the osteonecrosis pattern in this case can be classified as "en block."

Antimicrobial, regenerative, and biostimulation therapies were implemented to successfully treat BRONJ around an osseointegrated implant. The results showed noticeable PD reduction and radiographic bone regeneration at 2 years. This combined therapy, aimed at regenerating bone and soft tissues around osseointegrated implants, was successful for treatment of implant-associated BRONJ.

References

Al-Zoman KH, AlBAzie S, Robert AA*, et al.* Surgical management of bisphosphonate-related osteonecrosis of the jaw: Report of three cases. *Journal of Palliative Care* 2013; **29:**52-57.

Aoki A, Mizutani K, Schwarz F*, et al.* Periodontal and peri-implant wound healing following laser therapy. *Periodontol 2000* 2015; **68:**217-269.

Barres L, D.S. Mota A, Greenberg M, Almojaly S and Dziak R. Effects of alendronate on human alveolar osteoblastic cells: Interactions with platelet- derived growth factor. *International Journal of Dental and Oral Health* 2015; **1.2:**http://dx.doi.org/10.16966/2378-7090.108

Bassetti M, Schar D, Wicki B*, et al.* Anti-infective therapy of peri-implantitis with adjunctive local drug delivery or photodynamic therapy: 12-month outcomes of a randomized controlled clinical trial. *Clinical Oral Implants Research* 2014; **25:**279-287.

Basso FG, Pansani TN, Turrioni AP, Bagnato VS, Hebling J and de Souza Costa CA. *In vitro* wound healing improvement by low-level laser therapy application in cultured gingival fibroblasts. *International Journal of Dentistry* 2012; **2012:**719452.

Chadha GK, Ahmadieh A, Kumar S and Sedghizadeh PP. Osseointegration of dental implants and osteonecrosis of the jaw in patients treated with bisphosphonate therapy: A systematic review. *Journal of Oral Implantology* 2013; **39:**510-520.

Cortellini P and Tonetti MS. Improved wound stability with a modified minimally invasive surgical technique in the regenerative treatment of isolated interdental intrabony defects. *Journal of Clinical Periodontology* 2009; **36:**157-163.

Dogan GE, Demir T and Orbak R. Effect of low-level laser on guided tissue regeneration performed with equine bone and membrane in the treatment of intrabony defects: A clinical study. *Photomedicine and Laser Surgery* 2014; **32:**226-231.

Froum SJ, Froum SH and Rosen PS. A regenerative approach to the successful treatment of peri-implantitis: A consecutive series of 170 implants in 100 patients with 2- to 10-year follow-up. *International Journal of Periodontics and Restorative Dentistry* 2015; **35:**857-863.

Glowacki J. Bisphosphonates and bone. *Orthopaedic Journal at Harvard Medical School* 2005; **7:**64-65.

Hakki SS and Bozkurt SB. Effects of different setting of diode laser on the mRNA expression of growth factors and type I collagen of human gingival fibroblasts. *Lasers in Medical Science* 2012; **27:**325-331.

Javed F and Almas K. Osseointegration of dental implants in patients undergoing bisphosphonate treatment: A literature review. *Journal of Periodontology* 2010; **81:**479-484.

Khan AA, Morrison A, Hanley DA*, et al.* Diagnosis and management of osteonecrosis of the jaw: A systematic review and international consensus. *Journal of Bone and Mineral Research* 2015; **30:**3-23.

Kwon TG, Lee CO, Park JW, Choi SY, Rijal G and Shin HI. Osteonecrosis associated with dental implants in patients undergoing bisphosphonate treatment. *Clinical Oral Implants Research* 2014; **25:**632-640.

Lopez-Cedrun JL, Sanroman JF, Garcia A*, et al.* Oral bisphosphonate-related osteonecrosis of the jaws in dental implant patients: A case series. *The British Journal of Oral & Maxillofacial Surgery* 2013; **51:**874-879.

Madrid C and Sanz M. What impact do systemically administrated bisphosphonates have on oral implant therapy? A systematic review. *Clinical Oral Implants Research* 2009; **20:**87-95.

Martin DC, O'Ryan FS, Indresano AT*, et al.* Characteristics of implant failures in patients with a history of oral bisphosphonate therapy. *Journal of Oral and Maxillofacial Surgery* 2010; **68:**508-514.

Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic. *Journal of Oral and Maxillofacial Surgery* 2003; **61:**1115-1117.

Marx RE, Sawatari Y, Fortin M and Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: Risk factors, recognition, prevention, and treatment. *Journal of Oral and Maxillofacial Surgery* 2005; **63:**1567-1575.

Nevins M, Camelo M, Nevins ML, Schenk RK and Lynch SE. Periodontal regeneration in humans using recombinant human platelet-derived growth factor-BB (rhPDGF-BB) and allogenic bone. *Journal of Periodontology* 2003; **74:**1282-1292.

Nevins M, Giannobile WV, McGuire MK*, et al.* Platelet-derived growth factor stimulates bone fill and rate of attachment level gain: Results of a large multicenter randomized controlled trial. *Journal of Periodontology* 2005; **76:**2205-2215.

Nevins ML, Reynolds MA, Camelo M, Schupbach P, Kim DM and Nevins M. Recombinant human platelet-derived growth factor BB for reconstruction of human large extraction site defects. *International Journal of Periodontics and Restorative Dentistry* 2014; **34:**157-163.

Persson GR, Salvi GE, Heitz-Mayfield LJA and Lang NP. Antimicrobial therapy using a local drug delivery system (Arestin) in the treatment of peri-implantitis. I: Microbiological outcomes. *Clinical Oral Implants Research* 2006; **17:**386-393.

Petropoulos VC, Balshi TJ, Wolfinger GJ and Balshi SF. Treatment of a patient with implant failure and jaw osteonecrosis: Successful retreatment using implants. *The Journal of Oral Implantology* 2016; **42:**82-85.

Rao MV, Berk J, Almojaly SA*, et al.* Effects of platelet-derived growth factor, vitamin D and parathyroid hormone on osteoblasts derived from cancer patients on chronic bisphosphonate therapy. *International Journal of Molecular Medicine* 2009; **23:**407-413.

Ridgway HK, Mellonig JT and Cochran DL. Human histologic and clinical evaluation of recombinant human platelet-derived growth factor and beta-tricalcium phosphate for the treatment of periodontal intraosseous defects. *International Journal of Periodontics and Restorative Dentistry* 2008; **28:**171-179.

Ruggiero SL, Dodson TB, Fantasia J*, et al.* American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. *Journal of Oral and Maxillofacial Surgery* 2014; **72:**1938-1956.

Salvi GE, Persson GR, Heitz-Mayfield LJ, Frei M and Lang NP. Adjunctive local antibiotic therapy in the treatment of peri-implantitis II: Clinical and radiographic outcomes. *Clinical Oral Implants Research* 2007; **18:**281-285.

Sanz-Moliner JD, Nart J, Cohen RE and Ciancio SG. The effect of an 810-nm diode laser on postoperative pain and tissue response after modified Widman flap surgery: A pilot study in humans. *Journal of Periodontology* 2013; **84:**152-158.

Schar D, Ramseier CA, Eick S, Arweiler NB, Sculean A and Salvi GE. Anti-infective therapy of peri-implantitis with adjunctive local drug delivery or photodynamic therapy: Six-month outcomes of a prospective randomized clinical trial. *Clinical Oral Implants Research* 2013; **24:**104-110.

Sunkara S, Beneduce C and Andreana S. Socket preservation and implant insertion in a smoker with a 10-year history of bisphosphonate use: A case report. *Journal of Long-Term Effects of Medical Implants* 2010; **20:**327-334.

Trombelli L, Farina R, Franceschetti G and Calura G. Single-flap approach with buccal access in periodontal reconstructive procedures. *Journal of Periodontology* 2009; **80:**353-360.

Zahid TM, Wang BY and Cohen RE. Influence of bisphosphonates on alveolar bone loss around osseointegrated implants. *The Journal of Oral Implantology* 2011; **37:**335-346.