Dental Implant Placement with Bone Augmentation in a Patient Who Received Intravenous Bisphosphonate Treatment for Osteoporosis

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ABSTRACT

Intravenous (IV) administration of bisphosphonates has been considered an absolute contraindication for placement of dental implants, because of the increased risk of bisphosphonate-related osteonecrosis of the jaw (BRONJ). However, the evidence regarding this association originates from patients being treated for various forms of metastatic cancer. In the case reported here, a patient received a dental implant while undergoing IV treatment with zoledronic acid for osteoporosis. The authors discuss the current evidence regarding the risks of dental procedures in patients receiving IV bisphosphonates for this indication. They also evaluate important risk factors and the decision-making pathway in such cases. On the basis of existing evidence, receipt of a single IV infusion of zoledronic acid for the treatment of osteoporosis does not appear to be an absolute contraindication to implant placement.

Bisphosphonates reduce or even suppress osteoclast function and can therefore be used to treat various disorders that cause abnormal bone resorption. In the 1980’s, bisphosphonates administered by the intravenous (IV) route were initially used for the treatment of malignancies affecting the bone tissue, such as multiple myeloma and bone metastases of breast and prostate cancer. However, the relatively recent introduction of IV bisphosphonates for the treatment and prevention of osteoporosis has expanded the application of these medications to a significant proportion of the adult population. Loss of osseointegrated implants in association with bisphosphonate therapy was reported as early as 1995. Not surprisingly, early studies focused on positive outcomes from the use of these drugs in conjunction with implant therapy, such as increasing the contact between bone and implant. The possibility of a connection between use of bisphosphonates for cancer therapy and osteonecrosis of the jaw bones was first raised in 2003. Further studies in cancer patients confirmed the association between IV treatment with bisphosphonates and the condition later described as bisphosphonate-related osteonecrosis of the jaw (BRONJ). However, this association appears less clear where bisphosphonates are used for treatment or prevention of osteoporosis. Treatment of osteopenia and osteoporosis involves a much lower cumulative dosage than is the case for cancer therapy. Typically, the required dosage has been achieved by systemic oral administration, but IV administration is increasingly the treatment of choice.

Numerous papers in the dental literature have examined the risks of invasive dental procedures in patients being treated with oral bisphosphonates and have concluded that dental procedures are not contraindicated for such patients, the evidence being stronger for treatment of less than 5 years’ duration. In the case of IV administration, the few papers that have discussed this subject have usually considered this form of therapy to be an absolute contraindication for dental procedures, especially elective surgery such as dental implants. However, this conclusion is based on published research for patients with cancer and does not differentiate on the basis of purpose of treatment, type of medication, cumulative dose or duration of treatment.

The current manuscript describes a patient who was receiving treatment with IV bisphosphonates for osteoporosis and who was a candidate for dental implant placement and reviews the underlying evidence to support decision-making and treatment planning in similar cases.
Case Report

Examination

A 58-year-old man sought treatment at the authors’ clinic because of de-cementation of a post-and-core reconstruction in tooth 21 (Figs. 1a, 1b). Clinical examination revealed secondary caries, as well as a vertical fracture with subgingival margins in the palatal side of the root, accompanied by a localized periodontal pocket of 6 mm (Fig. 2). The patient had no pain or other symptoms but was very concerned about the esthetic problem and potential implications for his social and professional life.

Radiographic examination confirmed the fracture with subgingival margins and the secondary caries and also revealed a periapical radiolucency (Fig. 3). During the medical history-taking, the patient reported a recent diagnosis of osteoporosis and receipt of a single IV infusion of 5 mg of zoledronic acid 8 months before the current visit. The patient expected to receive a second infusion in approximately 4 months (i.e., 1 year after the first infusion). Otherwise, the patient was healthy.

Description of Treatment

The decision was made to extract tooth 21. After the extraction, the socket was curetted to remove granulation tissue (Figs. 4 and 5). The socket was left to heal without any sutures or further intervention. Healing was uneventful, without complaints, although slightly slower than expected. Six weeks after the extraction, an implant was placed according to the protocol for delayed-immediate placement. A midcrestal incision in the area of tooth 21, with a minor release incision, was performed under local anesthesia. After reflection of a mucoperiosteal flap, one implant (4.1 × 12 mm Bone Level Regular CrossFit implant, Straumann Basel, Switzerland) was placed, with simultaneous augmentation of the buccal bone (using Bio-Oss 0.25-mm xenograft granules and Bio-Gide resorbable membrane, Geistlich Pharma AG, Wolhusen, Switzerland). A cover screw was placed, and the implant was submerged for a healing period of 3 months. A video of the surgery and healing events is available at: http://youtu.be/LqyGGiHOU-o.
After the 3-month healing period, which was uneventful (Fig. 6), the implant was exposed with a biopsy punch, and a healing abutment was connected (Fig. 7). Two weeks later, the implant was restored with a cement-retained ceramic crown on a zirconia abutment (Figs. 8a-8e).

Figure 4: The extraction socket.

Figure 5: Granulation tissue attached to the apical region and the fracture line were visible after extraction of tooth 21.

Figure 6: Healing of the surgical site 3 months after placement of the implant.

Figure 7: Exposure of the implant and abutment connection.
Follow-up examination 6 months after implant placement showed no signs of pathology or alterations in the soft or hard tissues, and the patient had no subjective complaints. Further clinical and radiographic examination 1 and 2 years after surgery will be required to confirm the long-term success and stability of the implant. However, as the great majority of cases of BRONJ related to dental procedures have appeared as complications of postsurgical healing, it is reasonable to assume that major risks related to the procedure are no longer present. However, the potential for future occurrence of BRONJ in this patient cannot be excluded, especially if he undergoes further bisphosphonate treatment.

Discussion

In the case reported here, tooth 21 was deemed unrestorable because of a combination of factors, specifically, presence of a vertical fracture with deep subgingival margins, periapical radiolucency and secondary caries. Extraction would have been the obvious course of action under normal conditions; however, because the patient had received a single injection of zoledronic acid, more detailed consideration was required. Zoledronic acid is one of the so-called second-generation bisphosphonates and one of the most potent nitrogen-containing medications of this group. Pharmacokinetic data are not available for use of this drug in patients with osteoporosis. However, in 64 patients with cancer, post-infusion plasma concentrations of zoledronic acid decreased rapidly in the first 24 hours, and the terminal elimination phase was prolonged, with only small amounts of the drug still traceable after 48 hours. It was assumed that the balance of drug, presumably bound to bone, was slowly released back into the systemic circulation.

The use of bisphosphonates has been correlated with an increased risk of BRONJ after invasive dental procedures. Consequently, consideration of all decision-making factors in this case would include an evidence-based risk assessment, a risk–benefit analysis, and a review of the clinical conditions and the patient’s wishes.

Risk Assessment

Quantifying the risk of complications such as BRONJ in patients receiving bisphosphonates for osteoporosis is difficult, given the existing evidence. The estimated cumulative incidence of BRONJ among cancer patients treated by IV bisphosphonates reportedly ranges from 0.8% to 12%. Time of treatment appears to be an important factor, as the incidence of BRONJ increased from 1.5% among patients treated for 4 to 12 months to 7.7% among those treated for 37 to 48 months. On the basis of these data, some authors have recommended withholding all elective procedures from patients who are receiving IV bisphosphonates. However, as specified above, these figures originate from cancer patients whose treatment course is very different than for osteoporosis. Cancer treatment can involve multiple doses of bisphosphonates (often on a monthly, or more frequent, basis) and patients might receive an array of other medications, such as corticosteroids. Among patients with metastatic cancer in whom BRONJ occurred, the median number of treatment cycles was 35 and the median time of exposure to bisphosphonates was 39.3 months.
contrast, a study assessing once-yearly infusion of zoledronate for management of osteoporosis in 8000 individuals reported only one potential episode of BRONJ in each of the placebo and intervention groups, and both cases resolved with antibiotics and minor debridement.\textsuperscript{12} Three-year follow up of the same patients showed no incidence of BRONJ at all.\textsuperscript{20}

A recent systematic review concluded that a patient receiving oral bisphosphonates for a period of less than 5 years is “safe” to undergo dental procedures, specifically dental implants.\textsuperscript{14} However, the authors noted that 5 years of oral therapy could lead to higher cumulative concentrations than single IV doses of zoledronic acid (5 mg).

Overall, on the basis of these findings, the risk of complications such as BRONJ after a single IV infusion of zoledronic acid appears to be very low.

**Risk–Benefit Analysis**

A key problem that has affected the reported incidence of BRONJ in much of the existing research has been the definition of osteonecrosis, which was unclear and constantly changing until at least 2005. The main issue related to the length of time that wound-healing could be delayed before the condition was diagnosed as true osteonecrosis. Initial healing (i.e., re-epithelialization) of dental wounds, such as those related to dental extractions, usually takes 1 to 3 weeks. Taking into account that many of these patients had other medical conditions, had undergone radiotherapy or were receiving steroid therapy, prolonged healing (as long as 6 weeks) would not necessarily have been related to the osteonecrosis.

In 2009, a report from the task force of the American Society for Bone and Mineral Research defined a “suspected” case of osteonecrosis as “an area of exposed bone in the maxillofacial region that has been identified by a health care provider and has been present for less than 8 weeks”.\textsuperscript{19} BRONJ would be the definitive diagnosis only if 8 weeks elapsed without complete healing. The current criteria for a diagnosis of BRONJ are as follows:

- current or previous treatment with a bisphosphonate.
- exposure of bone in the maxillofacial region persisting for more than 8 weeks.
- no history of radiotherapy to the jaws.

An attempt has also been made to define clinical stages of osteonecrosis of the jaw:\textsuperscript{21}

- **Stage 1**: Asymptomatic presence of exposed or necrotic bone, with no evidence of infection.
- **Stage 2**: Presence of exposed necrotic bone, accompanied by infection and erythema, with or without purulent discharge.
- **Stage 3**: Presence of all stage 2 characteristics with additional features, such as pathological fracture, draining sinus or communication (either intra-oral or extra-oral), and osteolysis.

More recently, stage 0 has been added for patients with signs of osteonecrosis of the jaw but no exposed bone.\textsuperscript{19}

Although BRONJ is a significant complication, it is in most cases manageable and, according to some authors, even preventable.\textsuperscript{22} Frequent preventive dental examinations, combined with identification of patients at risk and optimal oral hygiene,\textsuperscript{8} can improve outcomes and reduce the incidence of BRONJ.\textsuperscript{22} The management of BRONJ usually involves conservative antibiotic therapy, debridement of the wound and removal of all necrotic bone segments, administration of medications for symptomatic relief, optimal oral hygiene and local use of chlorhexidine-containing antiseptic mouth rinse.\textsuperscript{23} Among patients receiving oral bisphosphonate therapy, BRONJ only rarely progresses beyond stage 2.\textsuperscript{24} In one case of BRONJ that developed after extraction of a molar, the patient had been treated with alendronate for 5 years, and healing was achieved after the treatment was changed from alendronate to teriparatide.\textsuperscript{25} A typical clinical manifestation of BRONJ, with exposure of necrotic bone tissues, is shown in Fig. 9. After debridement of the wound and removal of the necrotic bone segments (Figs. 10 and 11), the wound is sutured for primary healing, ensuring good coverage of the underlying bone (Fig. 12).

A biopsy sample taken from a core BRONJ lesion would reveal only osteonecrosis, as suggested by the presence of “empty” osteocytes. However, the immediate perilesional zone would show dying osteocytes, necrotic detritus, hemorrhage and a robust inflammatory infiltrate of lymphocytes and plasma cells. Remarkably, in some visual fields, a significant number of osteoclasts are seen on the bone surface. If present in large numbers, these cells could aggravate the bone decay characteristic of this condition (Fig. 13).

Some recent studies have suggested that reduced serum levels of C-terminal telopeptide can determine osteoclast suppression and may predict the risk of development of BRONJ after dentoalveolar surgery.\textsuperscript{26} However, it remains to be seen if such serum markers have clear predictive value, as the few research reports available have presented conflicting results.\textsuperscript{27}
Specific Clinical Conditions

In the case reported here, evaluation of the specific clinical conditions indicated that further treatment of tooth 21 would have been inappropriate. Apart from the restorative problems, the periapical pathology was a concern, as BRONJ has been related not only to dental procedures but also to untreated dental pathology. In this regard, it is interesting to note that the single dental procedure that has been linked to BRONJ is extraction of a tooth. Consultation with the patient’s physician is an essential step in decision-making, although the main responsibility lies with the operating dentist. After comprehensive risk assessment, and provided the patient deems the risks acceptable, proceeding with the extraction would be the first step, as this procedure is essential for the patient’s health. In the current case, the uneventful healing was seen as a positive sign for proceeding with the implant, although it did not in any way guarantee that implant placement would also be free of complications, since the possibility of later occurrence of BRONJ could not be excluded.

To the authors’ knowledge, this is the only published report of implant placement in a patient treated with IV zoledronate for osteoporosis. In 2 previous case reports, patients with Paget’s disease who were being treated with IV bisphosphonates received dental implants without any signs of BRONJ, whereas other case reports have described successful implant placement for rehabilitation of damage caused by BRONJ in patients treated for cancer.

For the patient described here, one more dose of zoledronic acid was likely to be required in the months following implant placement, and it could be that timing of dental procedures in relation to dose administration is important. As such, it might be preferable to complete all required dental procedures before the second dose, to minimize the risks. The development of osteonecrosis of the jaw has been linked to longer duration of exposure to bisphosphonates, and hence higher cumulative dose and prolonged survival, as well as concurrent therapy, such as prednisolone or thalidomide use.

Once a decision has been made to place an implant, the general precautions for an atraumatic procedure must be observed. Primary coverage of the wound (to allow submerged healing of the implant) may also be of benefit. It would be preferable to avoid substantial augmentation, but esthetic considerations may necessitate some buccal augmentation procedures.

There is little evidence supporting the use of antibiotics in conjunction with implant placement in cases such as this one, although
Conclusions

Because IV infusion of bisphosphonates is increasingly used for the treatment of osteoporosis, it is important to differentiate the risk of such therapy from the risks related to treating cancer with these drugs. On the basis of existing evidence, receipt of a single IV infusion of zoledronic acid for the treatment of osteoporosis does not appear to be an absolute contraindication to implant placement.

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References

27. Fleisher KE, Welch G, Kottal S, Craig RG, Saxena D, Glickman RS. Predicting risk for bisphosphonate-related osteonecrosis of the jaws: CTX


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