Case Report

Dental Implications of Osteogenesis Imperfecta: Treatment with IV Bisphosphonate: Report of a Case

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Abstract: *Osteogenesis imperfect (OI) is a group of genetically diverse connective tissue disorders. Bisphosphonates therapy to manage bone fragility, a now common medical therapy for OI, can increase the risk of bisphosphonate-associated osteonecrosis of the jaws. In this report, a 6 ½ year child, who was receiving bisphosphonate therapy for OI, underwent full mouth dental rehabilitation in the operating room while under general anesthesia. The child had numerous teeth restored and multiple primary molar extractions. The patient, who received prophylactic antibiotics intraoperatively, demonstrated no clinical signs of bisphosphonate-associated osteonecrosis when seen at follow-up. Although bisphosphonate osteonecrosis is a possible sequel in children who receive multiple extractions, no clinical signs were manifested in our patient, who required multiple primary tooth extractions along with restorative treatment under general anesthesia. While no dental guidelines have been developed to manage OI children having been treated with bisphosphonates, consent for extractions should include the risk of bone necrosis and careful post-operative observation to monitor wound healing.*
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Osteogenesis imperfecta (**OI**) is often caused by type I collagen mutations and has both connective tissue and extraskeletal manifestations. For example, low bone mass with concomitant bone fragility can occur in combination with other tissues such as tendons, skin, meninges, ligaments, teeth (dentinogenesis imperfecta [**DI**]), and sclera. Hearing impairment has also been reported.[1-4] The clinical severity of OI is a wide spectrum ranging from lethality in utero to mild osteopenia and a modest increased fracture risk.[1-4]

OI is genetically heterogeneous and can be transmitted as an autosomal dominant, autosomal recessive, or as a sporadic trait, with a relatively high prevalence of new dominant mutations. The incidence of OI ranges from 1:5,000 to 1:20,000 live births, although the exact incidence is unknown. OI appears to have a similar prevalence in diverse racial and ethnic populations.[2-5] In parallel with the clinical spectrum of the disease, the molecular basis of OI is similarly diverse with collagen (eg, COLA1 and COLA2) genes being involved and a multitude of mutations having been identified.[1-4] Genes encoded for leprechaun, cartilage-associated protein, and peptidyl-prolylisomerase B also are associated with different forms of OI.

The most commonly used classification system distinguishes among 4 of the 9 known clinical types of OI, for which standard genetic testing can confirm the presence of the disease and represents approximately 90% of OI cases.[6-8] For example, type I OI is a milder form with no major bone deformities and affected individuals usually reaching normal stature. Hearing loss is relatively common, and the sclera of affected individuals is typically blue; DI may not be present.[6-8] Type II OI, by contrast, has a severe phenotype and is often lethal in utero or in the perinatal period due to respiratory failure associated with multiple rib fractures.

Individuals with type III OI characteristically have short stature and failure to thrive. These children present with multiple bone fractures that result in both limb and spine deformities (eg, vertebral compression fractures), and both hearing loss and DI are relatively common.[6-8] Type IV OI patients can also have short stature, albeit more variable, and present with moderate bone deformities, typically have white sclera and a variable presentation of both hearing loss and DI.[6-8] When classic features of OI are present, the clinical diagnosis can be relatively straightforward; however, confirmation by genotyping and/or determination of collagen production in fibroblasts may be required.

OI patients also can possess distinctive facial characteristics. For example, the OI phenotype often manifests with a triangularly shaped face, an overhanging occiput, and significant frontal bossing.[3,9] Most adult patients (75%, as reported by Kindelan in 2003) demonstrate Class III malocclusion, and ectopic eruption of the first and second molars is also common. When DI is present with OI, the teeth are discolored, ranging from amber-brown to blue-gray or yellow. The teeth have an opalescent sheen and frequently demonstrate severe attrition subsequent to cracking and loss of enamel. The primary dentition is usually affected to a greater degree than the secondary dentition.[3,9] Radiographically, the crowns are

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bulbous in shape and posses a significant cervical constriction, the roots are often short and peg-shaped, and the pulp chambers and canals will, over time, typically become increasingly obliterated.[3,9]

The underlying defect in OI involves a variety of cells producing an abnormal extracellular matrix (type I collagen) that functions aberrantly during mineralization of the bone and teeth and has altered physical properties in tissues such as ligaments, skin and sclera. Traditional treatment options have, to date, addressed primarily abnormal bone mineralization given the lack of genetic therapy for OI. Consequently, the treatment strategy is, by definition, palliative and not curative, with the primary goals being to reduce bone pain, bone fragility, fracture incidence, and concomitant bone deformity.[3,4,10] Clearly, achieving these goals will have a marked positive impact on the individual's quality of life. Rehabilitative physical therapy, occupational therapy (including aquatherapy), hearing augmentation, and orthopedic surgery have been the traditional treatment modalities. Medical management directed at increasing bone mineral density and reducing fracture risk, however, has demonstrated benefits and is now a relatively common therapy for OI patients.[3,4,10]

One current common medical therapy for OI involves bisphosphonates. The effects of this class of drugs on bone and calcium metabolism was discovered nearly 40 years ago. Bisphosphonates have been used principally in the treatment of myeloma, bone metastasis, Paget disease of the bone and osteoporosis in adults.[6,7] Bisphosphonates are structural analogs of inorganic pyrophosphate.[6,7] They act to promote increased bone density by at least 2 mechanisms—as structural analogues of pyrophosphate, they: (1) incorporate into mineralized bone; and (2) inhibit bone resorption by osteoclasts.[6,7,10] Some bisphosphonates, particularly those with nitrogen side chains (eg, pamidronate, aldendronate, and risedronate) also inhibit farnasyl transferases, a key class of enzymes that function in a number of osteoclast signal transduction pathways. The effects of bisphosphonates on osteoblasts are less well delineated, but may alter the formation of osteoblast precursors. Although orthopedic deformities still require corrective surgery, bisphosphonates are indicated for symptomatic treatment of OI in children by virtue of their ability to decrease bone pain and fracture rate and improve mineral density.[6,7,10]

Bisphosphonates can be administered either orally or intravenously. The most widely used regimen in pediatric OI was pioneered by Glorieux et al. and involves intravenous pamidronate over a 3-day cycle, for which the dose and cycle interval vary with the child's age, and is now initiated in infancy.[2,11,12,15]

Side effects occur with both oral and IV routes of administration. The oral route (eg, alendronate) has variable bioavailability and can be associated with gastrointestinal side effects.[2,11,12,15] With intravenous administration (eg, pamidronate) there is typically an acute reaction during the first administration that is characterized by fever, musculoskeletal pain, edema, and hypocalcemia.[2,11,12,15] Other side effects include thrombophlebitis, hyperlipidemia, hypothyroidism, uremia, elevated hepatic enzymes, and microcytic anemia.

By contrast, long-term sequela, although less clear, has been the source of recent concern. Given the extensive half-life of bisphosphonates, once the drug is incorporated into the bones of growing individuals, it is conceivable that any long-term sequela could take years to appear. For example, studies have reported that levels of pamidronate can be detected in the urine 8 years after drug administration. Concerns over such long-term "leaching" from bone exposed to pamidronate/alendronate include both potential effects during pregnancy as well as impaired fracture repair years after treatment.[2,3,6,11-13,16]

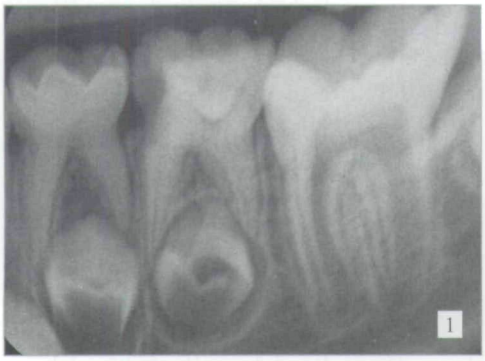
Most notable has been the concern of bisphosphonate regimens and a potential for increased risk of bisphosphonate-associated osteonecrosis (**BON**) of the jaws, especially given the extended timetable in which bisphosphonates are present in the bone.[3] This condition is most often associated with patients receiving chemotherapy and bisphosphonates to prevent bone metastasis of the primary lesion, frequently myeloma.[3] The incidence of BON is approximately 6/100,000 women (postmenopausal status post-chemotherapy) and has been reported in conjunction with dental implants.[17] The risk also appears to be greater with those women who received pamidronate compared to those treated with alendronate.[17] Although no incident of BON has been reported in children, this could be because of the extended duration of bisphosphonate action and, thus, BON may occur years later.[3]

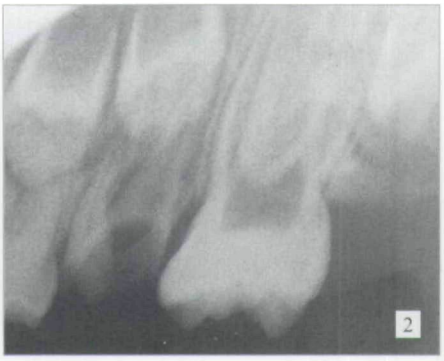
In relation to the oral cavity, BON can occur in either jaw, although it occurs slightly more frequently in the mandible.[13] At the onset, the signs and symptoms of BON can be vague. Initially, patients describe a sudden onset of oral discomfort or numbness, although there are no pathognomonic signs for BON.[12,13] Treatment of BON requires a team approach with long-term management. The first intervention involves a palliative approach using antibiotics (penicillin or clindamycin in addition to an oral antimicrobial rinse). These rinses (eg, chlorhexdine gluconate) may be needed for an indefinite period of time.[12,13]

The purpose of this report was to present the management of a child with osteogenesis imperfecta requiring dental extractions and who had been previously treated with pamidronate administered intravenously.

Case report. A 4-year, 8-month-old male of African American and Lumbee Native American descent presented to the Pediatric Dentistry Graduate Clinic at the University of North Carolina School of Dentistry in Chapel Hill, NC with a history of OI and DI. He was also positive for sickle cell trait and a family history significant for having a father and half-sibling with "fractures." Regarding his OI, the child had a history of multiple bone fractures, bilateral femoral osteotomies, and orthotics for his femoral bowing. The child was being treated with IV pamidronate that was initiated when he was 4-years-old. Due to severe dental attrition, he required extraction of both primary maxillary central incisors. The child did not return for follow-up until approximately 18 months later, when he presented with further attrition and caries which required multiple posterior stainless steel crowns as well as extractions (Figures 1 and 2).

At 6 years, 6 months old, the child received full-mouth dental rehabilitation in the operating room under general anesthesia. At the time of surgery, he had received a total of 8 pamidronate infusions (most recent dose was 60 mg of pamidronate IV) in addition to vitamin D and calcium supplementation. The child was nasally intubated and received 9 stainless steel crowns. In addition, both primary maxillary second molars and 1 primary mandibular second molar were extracted without complication. The mother was informed of the potential for bone osteonecrosis prior to the teeth being





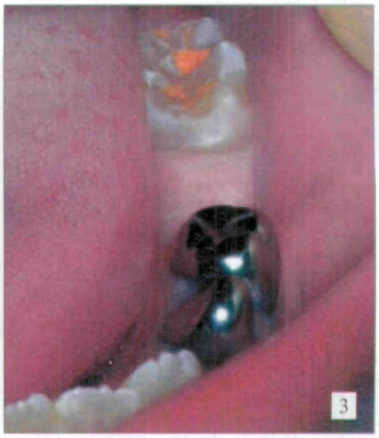


Figure 1. Intraoperative periapical radiograph in the lower left quadrant.
Figure 2. Intraoperative periapical radiograph in the upper left quadrant.
Figure 3. Healing extraction site.

extracted. The child was given ampicillin IV prophylactically immediately prior to surgery (50 mg/kg), as ordered by the child's physician. No antimicrobial rinses were prescribed for this patient, although that could have been used. A postoperative evaluation 1 month later demonstrated that all extraction sites were healing well with no clinical signs of BON (Figure 3). Currently, the child is more than 33 months post-treatment with no adverse sequela.

Discussion

Increasingly, oral health care providers are presented with patients with complex medical conditions that can require careful assessment of the potential risks of dental therapy and the need to manage those risks in providing the care. As illustrated in the present case, the clinician must stay abreast of current medical therapies for complex conditions and how these therapeutic approaches can impact oral health care delivery. OI patients have traditionally been a particularly challenging dental population to manage due to the combination of bone and dental issues. More specifically, OI patients with DI require dental extractions at a greater frequency due to the severe attrition that can occur secondary to enamel loss and poor mineralization of the dentin, as observed in the present case.

The incorporation of bisphosphonates into the medical treatment algorithm of OI presents potential management complications in the dental care of the patient. Informed consent should address the potential risk of BON. Further evidence indicates that administration of bisphosphonates via the IV route has a greater association with BON. Although the exact mechanism of bisphosphonates-induced BON is unclear, it is thought to be multifactorial.[12] Some of the factors thought to be involved in this process include the interaction between metabolism of bone, trauma, repair of bone, and infection.[12-15] For example, bisphosphonates have been reported to inhibit angiogenesis, and the frequency of bisphosphonate exposures is correlated with the incidence of developing BON.[12,14,15] Where osteoradionecrosis tends to be localized, however, osteonecrosis associated with bisphosphonates tends to be systemic.[13]

Most recently, the link between the use of bisphosphonates and osteonecrosis of the jaw has been reviewed in the *Journal of the American Dental Association*. Grbic et al., examined over 7,000 postmenopausal women with osteoporosis. In a placebo-controlled trial using zoledronic acid (5 mg IV), investigators found that an equal number of individuals in each group (1 per group) reported delayed healing associated with a maxillofacial infection, which resolved after systemic antibiotics with localized debridement. Their conclusion from this study was that osteonecrosis of the jaw is a rare event in postmenopausal women.[17] The risk of BON in the OI population remains unknown; however, there do not appear to be any published reports of BON occurring in OI sufferers at this time. This finding was also demonstrated by both Malmgren et al.,[18] and Schwartz et al.,[19] who examined 64 and 15 patients, respectively, all of whom had received bisphosphonates as part of their treatment for OI. None, however, developed osteonecrosis of the jaws.

Cortsos d Zavras examined the risk of osteonecrosis based on the route of bisphosphonate administration by reviewing claims data from greater than 700,000 individuals with either osteoporosis (generalized, postmenopausal, or idiopathic) or cancer (breast cancer, lung cancer, prostate cancer, or multiple myeloma). This information was cross-referenced with inflammatory conditions of the jaws. The authors concluded that if the bisphosphonate was administered via the intravenous route, there was a statistically significant increase ($P<.05$) in adverse jaw outcomes when compared to oral administration. In addition, they determined that the intravenous group also had a 4-fold increased risk for other inflammatory jaw conditions and a 6-fold increased risk of needing a major jaw resection.[20] Evaluation of tooth eruption in OI children shows that bisphosphonate therapy is associated with delayed tooth eruption of the permanent dentition.[21] Increased retention of the primary dentition could be associated with increased risk for dental abscess due to the increased longevity and attrition in the primary dentition.

In cases when surgical intervention is required, therefore, consultation with an oral maxillofacial surgeon is indicated. An attempt is made to keep surgical care as conservative as possible. In all cases, frequent long-term follow-up is necessary.[12-14] Also, since intravenous bisphosphonates have a half life that is measured in years, stopping them during management of BON would probably have little overall effect.[14,15] Finally, it should be noted that treatment recommendations are empirical, given the lack of long-term randomized controlled clinical trials.[15]

Finally, prevention of BON is obviously preferable to treating it. A dental consultation prior to the initiation of intravenous bisphosphonate therapy would be in order. A comprehensive examination and complete radiographic series should be completed so that any restorative procedures could be completed and nonrestorable teeth extracted prior to exposure to bisphosphonates.[12,14,15] Similarly, once bisphosphonate therapy has been started, dental treatment that can cause trauma to the soft tissues should be avoided whenever possible, whereas routine prophylaxis and restorative treatment can be performed for these patients. Higher risk procedures, such as extractions, require special attention with monthly post-op visits until the extraction site is completely healed.[12,14,15]

The potential risk of BON should be presented as part of the informed consent for extraction in patients that have received bisphosphonate therapy. While no specific guidelines exist for providing antibiotics for routine extractions in OI children who have been treated with bisphosphonates, routine prophylaxis may be prudent due to the effects of bisphosphonates on the bone vasculature and altered inflammatory response. Management of the bisphosphonates-treated OI child is now an issue for thousands of children, as this therapeutic approach has become the current standard of care. Additional studies are indicated to determine the most effective and safest approaches for delivering optimal oral health care to this population and to ultimately develop guidelines that can assist clinicians in managing the oral health of these children.

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