Resolution of Osteonecrosis of the Jaw After Teriparatide [Recombinant Human PTH-(1-34)] Therapy

ARTHUR N. LAU and JONATHAN D. ADACHI

J Rheumatol 2009;36;1835-1837
http://www.jrheum.org/content/36/8/1835

1. Sign up for TOCs and other alerts
   http://www.jrheum.org/alerts

2. Information on Subscriptions
   http://jrheum.com/faq

3. Information on permissions/orders of reprints
   http://jrheum.com/reprints_permissions

The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Resolution of Osteonecrosis of the Jaw After Teriparatide [Recombinant Human PTH-(1-34)] Therapy

To the Editor:

Although exceedingly rare in the population with postmenopausal osteoporosis, osteonecrosis of the jaw (ONJ) has a significant impact on the morbidity of the unfortunate patients who develop it. Currently recommended treatments have proven to be suboptimal, as many patients remain unresponsive.

We describe the second case of teriparatide therapy for treatment of ONJ that was unresponsive to conventional therapies.

Bisphosphonates are one of the most prescribed drugs in North America, with over 17 million prescriptions per year. There are several different indications for the use of bisphosphonates, and several forms are available, including an intravenous (IV) form (i.e., pamidronate and zoledronate) in the treatment of hypercalcemia in malignant diseases of bone such as multiple myeloma and breast cancer metastasis to the bone. IV bisphosphonates are also used in the pediatric population to treat osteogenesis imperfecta and idiopathic juvenile arthritis. Finally, the most common indication for bisphosphonates is in the treatment of osteoporosis, where an oral form is typically used (e.g., alendronate, risedronate).

Osteonecrosis of the jaw (ONJ) is a serious side effect of bisphosphonate therapy that has only been recently recognized. Since first described by Marx, et al in 2003, where 36 oncologic patients taking pamidronate or zoledronate presented with osteonecrosis of the jaw, hundreds of cases have been reported in cancer patients treated with IV bisphosphonates; but more recently, cases have also been reported in patients with osteoporosis treated with oral bisphosphonates. Based on current literature, 94% of patients with reported bisphosphonate-induced ONJ were treated with an IV form, while the remaining 6% were treated with an oral bisphosphonate. The estimated incidence of ONJ in patients receiving IV bisphosphonate therapy in the setting of multiple myeloma ranges from 4.5 to 12.8%, and from 1.2 to 12.0% in the setting of treatment of metastatic breast cancer.

 Patients with ONJ typically present with mandibular pain, purulent oral secretions, poor wound healing in the affected areas, and spontaneous intraoral tissue breakdown leading to exposure of necrotic maxillary or mandibular bone. Secondary infections may also occur (e.g., actinomycoses) resulting in osteomyelitis. Symptoms can range from negligible to severe, and often patients may be asymptomatic for weeks to months.

We describe a case of bisphosphonate induced ONJ that was unresponsive to conventional treatment and subsequently treated with teriparatide. Teriparatide [recombinant human PTH-(1-34)] is an anabolic agent shown to increase both bone mass and bone strength. Teriparatide was shown to be effective in the treatment of osteoporosis in the postmenopausal population and is currently an accepted treatment in severe osteoporosis, but it has not been widely used in the treatment of ONJ. Currently, there is one report of teriparatide in the treatment of ONJ. In our report, we review the current recommendations for treatment of bisphosphonate induced ONJ, and introduce several potential novel therapies, including the use of teriparatide.

Case presentation. A 56-year-old Caucasian woman was referred on June 6, 2005, for evaluation of localized alveolar necrosis of the right lower mandible. About one year prior she had multiple maxillary teeth removed in addition to one right mandibular tooth. Subsequently she did not heal well, developing chronic draining lesions, and recurrent alveolar bone chips persisted. This developed into local purulence and small areas of fistulation. Radiography showed localized alveolar necrosis that appeared to be limited to those sites.

Her medical history was positive for severe osteoporosis, diagnosed in 1995. She was believed to suffer from glucocorticoid induced osteoporosis, secondary to 18 months of prednisone use for her fibromyalgia. She was prescribed a variety of medications and still had numerous compression fractures of the spine. Her osteoporosis was initially managed with etidronate, but was discontinued due to her vertebral fractures. She was then started on Calcimar (salmon calcitonin) but this was replaced 6 months later with IV Clodronate (clodronic acid) due to lack of improvement in bone mineral density values. She showed improvements with Clodronate but subsequently her bone mass continued to decline, and she was switched to pamidronate for one year before having similar troubles. She was ultimately placed on monthly Zoledronate (zolendronic acid) in 2002. She remained on Zoledronate until March 2005 when she developed maxillary osteonecrosis and discontinued this medication.

Complete medical history includes asthma that was controlled with puffers and for which she had not received any recent prednisone. She also had underlying fibromyalgia, a hiatus hernia, osteoarthritis, and irritable bowel syndrome. Her medication list included: morphine SR (320 mg, once daily) for severe back pain secondary to vertebral compression fractures, amitryptiline (10 mg, once daily), Celexa (citalopram, 20 mg, once daily), estrogen (0.625 mg, once daily), Losid (omeprazole, 20 mg, once daily), ferrous gluconate (300 mg, once daily), Ativan (lorazepam) (0.5 mg Q6h PRN), Flovent (fluticasone, 125 PRN), Ventolin (albuterol, 100 µG PRN), Rhinocort (budesonide, 64 µG PRN), Novohydradizide (hydralazine, 25 mg, once daily), and Dilaudid (hydromorphone, 2-3 ml PRN).

Clinical examination revealed a well-developed, well nourished female. There was no facial swelling or asymmetry, and range of movement of the mandible was not limited. Examination of the pharynx revealed that she had had all of her upper teeth removed. There were also exposed bone chips in the right lower mandibular area where a tooth had been removed. She was in a great deal of pain from this particular area of exposed bone. This area was tender but looked reasonably healthy. No lymphadenopathy in the neck, supraclavicular, or axillary regions was noted.

Dental radiography showed alveolar necrosis that appeared to be localized to the right maxillary and mandibular areas (Figure 1). A computed tomographic (CT) study directed towards the mandible revealed a uniform and symmetric mandibular outline and medullary bone. In particular, there was no abnormality on the right side to which clinical attention was directed. The maxilla and hard palate were also visualized with no abnormal findings.

On April 29, 2005, she underwent the first surgical debridement of the right maxillary-mandibular area. Attention was drawn to the patient’s maxilla at which time a flap was raised from the right first molar area to the left first premolar area. A significant soft tissue and hard tissue defect was identified in teeth 1–3 (upper right molar), 1–2 (second molar), 1–1 (third molar) area. Obvious bone sequestra were evident intermixed with the soft tissue lesion. Debridement was performed down to what appeared to be healthy bone. The destruction appeared to involve some soft tissue in the right pyriform area at the floor of the nose. A similar area was treated in the same way on the posterior right mandible in 4–4 (lower right bicuspid) and 4–5 (first bicuspid) area.

CT study directed towards the mandible revealed a uniform and symmetric mandibular outline and medullary bone. In particular, no abnormality in the right side to which clinical attention was directed. The maxilla and hard palate also visualized did not reveal abnormal findings.

Pathology samples sent on April 29, 2005, consisted of 4 irregular fragments of soft and bony tan tissue 0.5 cm to 1.5 cm long. Specimens showed bony trabeculae surrounded by granulation tissue (Figure 1), a mixed inflammatory infiltrate and heavy bacterial/fungal colonization (Figure 2). Adjacent to these were several fragments of epithelium showing elongated anastomosing rete ridges with extensive neutrophil exocytosis. The feature of dead bone fragments is consistent with osteomyelitis, and the epithelial changes were interpreted to be reactive. The culture was positive for yeast-like organisms in addition to filamentous bacteria resembling actinomyces and Streptococcus intermedius, which is susceptible to penicillin.

She started various courses of oral amoxicillin 500 mg po bid, with only temporary reduction of inflammation and discharge. She was prescribed amoxicillin tid, but was unable to tolerate this dose due to recurrent abdominal pains. She received 10 day treatment courses, but her symptoms...
would typically relax within a few days. Her maximum course of amoxicillin was 10 days, and persistent pain and purulent discharge from the posterior right mandible continued. On November 13, 2005, she was restarted on amoxicillin 500 mg po bid for presumed actinomyces infection, this time for 3 months, as recommended for actinomyces infection.

At followup January 25, 2006, after several months of therapy there was no improvement and she developed another draining fistula in the posterior right mandible. Another local debridement was performed, which removed a large segment of necrotic bone and debrided the area that included a peripheral osteotomy.

Her zoledronate had been discontinued in March with no improvement in her osteonecrosis by January 2006. She was started on an 18 month course of the anabolic teriparatide (20 µg subcutaneous, sc, daily) in November 2005 to prevent fractures. She noticed improvement in her mandibular pain and ulcer healing about 2 months after starting teriparatide. After finishing her 18 month course, she reported completely healed oral ulcers and negligible pain from the site.

Although the exact mechanism of ONJ is unknown, osteoclasts play an essential role in turnover and remodeling of bone matrix; thus inhibition of osteoclastic activity by bisphosphonate is thought to contribute. Aminobisphosphonates (i.e., risendronate, alendronate) modulate the isoprenoid diphosphate lipid, which in turn inhibits the mevalonic acid pathway, and subsequently triggers osteoclast apoptosis. Osteonecrosis often occurs after a dental procedure, where the affected bone is unable to meet increased demand for bone turnover due to the inhibition of osteoclastic activity. However, some cases of ONJ occur spontaneously without associated trauma. Another possible mechanism for ONJ is based on bisphosphonate inhibition of angiogenesis, thus leading to decreased interosseous blood flow and subsequent remodeling impairment. Both inhibition of osteoclastic activity and impairment of angiogenesis may play a role in the mechanism of injury.

Risk factors that increase likelihood of developing ONJ include: use of high potency bisphosphonate, with the more potent zoledronic acid likely predisposing to ONJ; duration of use and total dose of bisphosphonate; advanced age; radiotherapy to the maxillofacial area; chemotherapy; steroid therapy; trauma; and surgical dental procedures.

Management of ONJ is challenging since effective treatments are lacking. Asymptomatic exposed bone is treated with systemic antibiotics such as penicillin or clindamycin, and oral antimicrobial rinse. Surgical intervention is limited to removal of loose segments of bony sequestra and sharp edges to prevent damage to adjacent soft tissues. There is no published data to support stopping IV bisphosphonates in cancer patients with established ONJ. This may be related to the long half-life of bisphosphonates in the skeleton, in particular alendronate and zoledronic acid.

Teriparatide (20 µg sc daily) was introduced by Harper et al for ONJ unresponsive to conventional therapy. The report described a 75-year-old woman taking Fosamax (alendronate, 70 mg once weekly) for primary osteoporosis. After 3 months of teriparatide therapy, a significant reduction in the size and number of ulcersations of the mandibular alveolus was noted, and a significant increase in bone regeneration of the extraction sockets was seen on a panoramic radiography. After 10 months of therapy, repeat radiography revealed completely healed extraction sites along with normal appearing oral mucosa. Teriparatide has been shown to directly stimulate bone growth, and also has a positive effect on the non-BMD determinants of bone strength.

The currently recommended treatments for ONJ are suboptimal, with many patients remaining unresponsive. We describe the second report of teriparatide treatment for ONJ otherwise unresponsive to conventional therapies. Although osteonecrosis resolved in both cases; the efficacy of teriparatide treatment for ONJ remains unproven. However, future research on teriparatide in ONJ may be of interest.
REFERENCES