Medication-Related Osteonecrosis of the Jaws From Once Per Year Intravenous Zoledronic Acid (Reclast): Report of 4 Cases

ARTICLE in IMPLANT DENTISTRY · FEBRUARY 2015
Impact Factor: 1.18 · DOI: 10.1097/ID.0000000000000227 · Source: PubMed

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Medication-Related Osteonecrosis of the Jaws From Once Per Year Intravenous Zoledronic Acid (Reclast): Report of 4 Cases

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Osteonecrosis of the jaws is a commonly reported side effect with patients prescribed oral antiresorptive medications (formerly known as bisphosphonates) to treat osteoporosis and osteopenia.1,2 Oral antiresorptive agents are considered as the standard of care for the prevention and treatment of women with postmenopausal osteoporosis and are the most widely prescribed medications for this skeletal disorder. Unfortunately, the entire dental profession is confronted with this adverse side effect because of established medical therapy in the management of osteoporosis and the complications of skeletal-related events.3,4

Oral medications approved by the United States Food and Drug Administration (FDA) include the following antiresorptive agents: Alendronate sodium (Fosamax; Merck & Co., Inc., Whitehouse Station, NJ); Risedronate sodium (Actonel, Warner Chilcot, Dublin, OH); and Ibandronate sodium (Boniva, Roche Group, South San Francisco, CA).7 Each of the medications differs in their binding affinity to bone, potency, and duration.8,9

For patient’s convenience and individuals unable to comply with a set dosing schedule of the antiresorptive medications, which may require once-weekly (Fosamax and Actonel) or once-monthly (Boniva) oral ingestion, a new once a year intravenous (IV) infusion of zoledronic acid was recently introduced in the management of osteoporosis. Reports of medication-related osteonecrosis of the jaw (MRONJ) have been reported in patients with cancer treated with multiple doses of IV zoledronic acid. However, there is a paucity of reports occurring with the once-yearly infusion of zoledronic acid (Reclast) for the management of osteoporosis. In this article, we report 4 cases of patients who had a history of long-term oral antiresorptive therapy and now were taking the once-yearly IV zoledronic acid (Reclast) and soon developed MRONJ after completing surgery of the maxilla and mandible. (Implant Dent 2015;24:227–231)

Key Words: zoledronic acid (Reclast), osteoporosis, medication-related osteonecrosis of the jaws
MRONJ has been reported in patients with cancer treated with multiple doses of IV zoledronic acid.\textsuperscript{22,23} The incidence of MRONJ for patients taking the IV form of this medication is estimated at 2\% to 18\%.\textsuperscript{24,25} In contrast, Merck et al estimate the risk of developing MRONJ for patients taking the oral form of antiresorptive agents is 0.7 cases per 100,000 person-years of exposure.\textsuperscript{16} The AAOMS position paper on MRONJ estimate the incidence of ONJ cases for patients taking the oral form as 0.01\% to 0.04\%.\textsuperscript{15,26} However, there are very few reports in the English literature of this occurring with the once-yearly infusion of zoledronic acid (Reclast, Novartis Pharmaceuticals; Aclasta, Novartis Pharma) for the management of osteoporosis.\textsuperscript{27,28} It is estimated that the risk of developing MRONJ from IV zoledronic acid in the management of osteoporosis is approximately 0.017\% (1.7 cases per 10,000 patients).\textsuperscript{29} In this article, we report 4 cases of patients who had a history of long-term oral antiresorptive therapy and now were taking the once-yearly IV zoledronic acid (Reclast) and soon developed MRONJ after completing surgery of the maxilla and mandible.

### Patients and Methods

For all clinicians, it is important to obtain a complete health history regarding patient exposure to antiresorptive agents.\textsuperscript{29} A prospective chart review of 4 patients was completed. Data included gender, age, systemic factors, duration of antiresorptive therapy (oral and IV) prescribed by their physician, jaw location of osteonecrosis, surgical treatment (debridement, sequestrectomy, platelet-rich plasma), and overall outcome. The study group consisted of 4 female patients whose age ranged from 70 years to 89 years. The mean age was 79.5 years (Table 1).

We adhere to the classification of the AAOMS\textsuperscript{15,26} to define MRONJ that consist of 4 stages (0–3) (Table 2). This clinical staging system has been established to define the severity of MRONJ and guide the clinician in the management of this surgical problem. Biopsy specimens were obtained from all 4 patients that were histopathologically diagnosed with actinomyces (Fig. 1). Of the 4 patients, 3 presented with stage 2 disease and 1 (mandible fracture) with stage 3 disease. One patient completed the sinus lift elevation procedure with bone graft augmentation of the right maxillary sinus in preparation for implant placement that became infected 2 weeks after the surgical procedure. Acute sinusitis and fistula formation were present upon initial examination. The other 3 patients had molar teeth extracted from the posterior maxilla and mandible. Oroantral communication was observed in the patient who had teeth extracted from the left

### Table 1. MRONJ Patient Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Complication</th>
<th>Time to Event (wk)</th>
<th>Stage</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>AK</td>
<td>F</td>
<td>87</td>
<td>Maxillary infection</td>
<td>1</td>
<td>2</td>
<td>Extraction of teeth</td>
</tr>
<tr>
<td>JK</td>
<td>F</td>
<td>72</td>
<td>Mandible infection</td>
<td>5</td>
<td>2</td>
<td>Extraction of teeth</td>
</tr>
<tr>
<td>BS</td>
<td>F</td>
<td>70</td>
<td>Sinusitis of right maxillary sinus</td>
<td>2</td>
<td>2</td>
<td>Sinus lift elevation with bone grafting</td>
</tr>
<tr>
<td>JS</td>
<td>F</td>
<td>89</td>
<td>Mandible fracture</td>
<td>2 (infection) 4 (fracture)</td>
<td>2</td>
<td>Extraction of teeth</td>
</tr>
</tbody>
</table>

**Average age:** 79.5 years.

**Time to Event:** From day of surgery to first observed postoperative signs and symptoms of MRONJ based on 2014 AAOMS classification.

**Stage:** Clinical signs and symptoms of MRONJ based on 2014 AAOMS classification.

### Table 2. MRONJ Staging and Treatment Strategies

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Nonspecific clinical findings, radiographic findings, and symptoms. No clinical evidence of necrotic bone</td>
<td>Systemic management. Use of analgesics and antibiotics</td>
</tr>
<tr>
<td>1</td>
<td>Asymptomatic, but exposed, necrotic bone or fistulas are present. No evidence of infection</td>
<td>Use of chlorhexidine mouth rinse, close monitoring of patient on quarterly basis. Provide patient education</td>
</tr>
<tr>
<td>2</td>
<td>Exposed necrotic bone or fistulas that probe to bone in area of infection. Clinical signs of infection, such as pain, erythema with or without purulent discharge</td>
<td>Symptomatic treatment with antibiotics, oral bacterial mouth rinse, pain control, debridement of infected area</td>
</tr>
<tr>
<td>3</td>
<td>Exposed necrotic bone or fistulas present that probes to bone and extends beyond region of alveolar bone, such as to inferior border of mandible, ramus of mandible, and zygoma in maxilla. Fracture of jaw or osteolysis present in jaws</td>
<td>All of the above treatment with more aggressive surgical intervention, such as debridement and resection of jaw</td>
</tr>
</tbody>
</table>

Staging and treatment strategy of MRONJ according to the position paper of the 2014 AAOMS.
posterior maxilla as the floor of the maxillary sinus was eroded. The 89-year-old patient sustained a mandible fracture 4 weeks (Fig. 2) after extraction of the teeth and a debridement procedure. All 4 patients (including the patient with the mandible fracture) were treated with surgical debridement that consisted of excision of all necrotic-appearing bone cellular therapy consisting of platelet-rich plasma and long-term oral antibiotic therapy for a period of 4 to 12 months prescribed by an infectious disease specialist.

**DISCUSSION**

Antiresorptive agents decrease bone resorption and skeletal fracture by chemically binding to calcium hydroxyapatite in the mineral phase of bone. They are attracted to areas of bone remodeling, where osteoclast activity is high and concentrating in the lacunae of the osteoclast. Therefore, the osteoclastic cell is the main target for antiresorptive agents and prevents osteoclasts from binding to the surfaces of bone, which prevents bone resorption and increases bone mineral density.30–33

IV infusion of zoledronic acid (Reclast) 5 mg over a 15-minute interval is used in the management of osteoporosis.2,10,11,34 It is considered as the most potent of the antiresorptive medications with a long half-life.10 In several human and animal studies, yearly IV doses of zoledronic acid had a greater effect on bone remodeling compared with oral antiresorptive medications and may be responsible for one of the many proposed mechanisms of MRONJ.34–36 However, clinical data regarding the incidence of MRONJ from once a year infusion of zoledronic acid (Reclast) is sparse.28,37 Data regarding our case series are presented in Table 1. All 4 patients were Asian women, with an average age of 79.5 years. They all had a positive history of long-term Fosamax (Merck, Whitehouse Station, NJ) use for over 10 years before treatment with IV zoledronic acid. Three of the 4 patients received 2 doses of zoledronic acid. The woman who developed a mandible fracture received only a single dose of zoledronic acid.

We hypothesize that all of our patients developed MRONJ while on IV zoledronic acid. Based on past clinical experience, it is the authors’ opinion that compared with the oral form of MRONJ, osteonecrosis of the jaws from the IV form of bisphosphonates presents with greater challenges. Of the 4 patients, 1 developed an infection that progressed to a mandible fracture 4 weeks after the teeth were extracted. The infection was refractory to surgical treatment, which ultimately required application of a reconstruction bone plate to stabilize the fracture segments once the fracture was identified.

Currently, it remains unclear if actinomyces is primarily involved in the pathogenesis of osteonecrosis in the patient on antiresorptive therapy.38–42 In Marx’s series of 30 consecutive MRONJ cases, they demonstrated high number of actinomyces species, but the clinical significance of this observation was not addressed.39 In a study by O’Ryan et al,43 actinomyces was present in greater than 75% of histologic specimens. When histopathology was available, LazaroVici et al48 reported that actinomyces colonies were identified.
93% of the time. In our opinion, recognition of actinomycosis is critical. The reasons for the use of the term "critical" are the facts that in the presence of signs and symptoms of soft tissue edema, erythema, orocutaneous fistulas, and suppuration in the MRONJ patient, actinomycosis should be recognized as a primary diagnosis and specific treatment directed at eradication of this bacterial pathogen. Therefore, our treatment regimen consists of penicillin VK at a dose of 1 g 3 to 4 times per day over a 4- to 12-month duration. If patients are younger than 65 years, probenecid, 500 mg 3 to 4 times per day is added to decrease antibiotic renal clearance. For patients who are allergic to penicillin, an alternative regimen such as doxycycline 100 mg twice daily, erythromycin 500 mg or clindamycin 300 mg 4 times per day is acceptable over 6- to 12-month duration.

Based on our surgical experience and that of others, surgical intervention should be considered early in the course of management of MRONJ. It has been demonstrated that conservative management in many advanced cases (Stage 2 and 3) results in only a 50% resolution defined as closure of the oral mucosa and remains refractory to conservative treatment. Surgical intervention may result in a more definitive treatment and resolution of MRONJ.

**Conclusion**

In this report, we describe 4 patients with a medical history of long-term oral antiresorptive therapy who were now taking the once-yearly infusion of IV zolendronic acid who soon developed MRONJ after completing surgery of the jaws. We anticipate that the dental practitioner will increasingly encounter patients not only prescribed the oral form of antiresorative agents but also the IV form as well and should be able to anticipate the potential complications from this medication.

**Disclosure**

The authors claim to have no financial interest, either directly or indirectly, in the products or information listed in the article.


