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Treatment of bisphosphonate-related osteonecrosis of the jaws: presentation of a protocol and an observational longitudinal study of an Italian series of cases

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Abstract

The aim of this study was to evaluate the efficacy of a treatment protocol for bisphosphonate-related osteonecrosis of the jaws (BRONJs). We conducted a longitudinal observational non-controlled study in 94 patients with confirmed BRONJ. Treatment was in two phases: supportive (antimicrobial mouth rinses, antibiotics, and anti-inflammatory steroids) to minimise infection and pain before the formation of a bony sequestrum; and surgical plus pharmacological treatment (sequestrectomy with antibiotic prophylaxis) after the sequestrum had developed. We did a Kaplan–Meier analysis (survival curve) to evaluate the time from the initial assessment until the formation of the bony sequestrum (endpoint), and a log-rank (Mantel–Haenszel) test to compare the formation times of the sequestra in men and women. Ninety-one of the 94 patients developed sequestra and were operated on. Three patients were withdrawn from the study because of severe pain and were treated by debridement before the sequestra developed. The results showed that sequestra developed within 15 months in all 91 patients. The Kaplan–Meier analysis showed that the mean time to formation of a sequestrum was 8 months (range 5–11). The difference between the mean time for men (5 months, range 2–8) and women (9 months, range 6–12) was highly significant ($p < 0.0001$). Within the limits of this study, we conclude that by waiting for the formation of bony sequestra while controlling infection and pain, it is possible to do a conservative resection, unless pain is severe or there is a risk of fracture. This non-aggressive approach permits the removal of all necrotic bone, avoids damage to adjacent healthy bone, and does not result in recurrences.

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Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a relatively rare but potentially serious complication of treatment with bisphosphonates. It is defined as the presence of exposed bone in the oral cavity that does not regress within 8 weeks in a patient who is currently, or has previously been, treated with bisphosphonates and who has not had radiotherapy to the craniofacial region. It is classified in 3 stages

based on clinical signs and symptoms.^{1,2} Recently stage 0 was added, to include high-risk patients with no clinical evidence of necrotic bone but with non-specific clinical signs and symptoms.²

Bisphosphonates are a class of pharmaceutical agents that are used to treat numerous bone disorders, including osteoporosis, metastases in the bone, and multiple myeloma. Their mechanisms of action involve osteoclastic apoptosis, inhibition of osteoblast-mediated osteoclastic activity, and the inhibition of neoangiogenesis,^{2,3} the result of which leads to the inhibition of bone turnover.^{1–3}

The most commonly reported initiating factor for BRONJ is tooth extraction, although periodontal disease and damage by dentures have been implicated. The risk is related

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to the relative potency of the individual drug; the amino-bisphosphonates, such as zoledronate and pamidronate, are more potent than the non-aminobisphosphonates, such as clodronate. The longer the duration of treatment, the greater the risk.^{2–4} According to the guidelines of the American Association of Oral and Maxillofacial Surgeons (AAOMS): “The treatment objectives for patients with an established diagnosis of BRONJ are to eliminate pain, control infection of the soft and hard tissue, and minimize the progression or occurrence of bone osteonecrosis”. The guidelines suggest that a surgical approach is indicated only in patients with advanced stages (stage 3 disease, and patients with stage 2 disease which is refractory to antibiotics).²

In this paper we report a protocol for the treatment of BRONJ as used for a series of patients with an established diagnosis of BRONJ.

Patients and methods

This is an observational, longitudinal, uncontrolled study of a series of patients with an established diagnosis of BRONJ who were treated according to an established protocol.

Between June 2008 and January 2010, 164 patients with BRONJ were referred to our Centre for Research, Prevention and Treatment of bisphosphonate-related osteonecrosis of jaws.

Panoramic radiography was the first diagnostic examination.

The exclusion criteria were: allergy to penicillins or ibuprofen; an existing bony sequestrum (diagnosed clinically or radiographically, or both) and exposed necrotic bone extending beyond the region of the alveolar bone, inferior border, and ramus in the mandible, maxillary sinus, and zygoma in the maxilla (stage 3). Ninety-four patients were selected, 91 of whom were included. The patients were informed about the treatment and signed a medical disclosure and consent form. Ethical approval was obtained for the study.

Data

The following variables were recorded: sex, age, bisphosphonates given, and time that elapsed between the initial evaluation and the formation of the bony sequestrum.

Statistical analysis

A parametric analysis of variance (ANOVA) was used to calculate the mean age. A Kaplan–Meier analysis (survival curve) was used to evaluate the time between the initial evaluation and the formation of the bony sequestrum (the endpoint). A log-rank (Mantel–Haenszel) test was used to compare the times of formation of bony sequestra in men and women.

Investigations

The radiographs consisted of panoramic radiographs, which were taken every six months to evaluate the osteonecrotic areas, and a computed tomographic (CT) dental scan, which was done only for patients who, during follow-up, had clinical or radiological signs that a sequestrum had formed. Panoramic radiographs were also taken postoperatively after 6 months for patients who had been operated on.

Treatment protocol

All patients had scaling and root planing, and were instructed to maintain optimal oral hygiene.

Treatment involved two phases. The first phase was supportive, to minimise infection and pain, anticipating the formation of a bony sequestrum. Follow-up was monthly, to evaluate the progression of the osteonecrotic lesions and to monitor the degree of inflammation of tissue. An antimicrobial mouth rinse was prescribed (povidone iodine 10% or chlorhexidine 0.12%). Piperacillin/tazobactam 2 g 12-h intramuscularly for 5 days, and ibuprofen 800–1200 mg/day for 3 days, were prescribed when there were signs of acute inflammation and increased pain.

The second phase was introduced when a bony sequestrum was clinically or radiographically diagnosed. The patient was admitted to hospital and given imipenem/cilastatin 500 mg/12-h intravenously for two days. This was followed by operation under general or local anaesthesia that comprised raising of mucoperiosteal flaps, extraction of involved teeth, sequestrectomy, curettage, antimicrobial irrigation of the surgical site, and suture of the flaps with 2/0 silk. All bony sequestra that were removed were examined histologically.

Postoperatively patients were given imipenem/cilastatin 500 mg 12-h intravenously for 3 days and, after discharge, piperacillin/tazobactam 2 g 12-h intramuscularly for 7 days. An antimicrobial mouth rinse was started 24 postoperatively. Sutures were removed after 15 days.

The postoperative follow-up was daily for the first week, weekly for the following month, and monthly thereafter for 6 months.

Results

Ninety-four patients were selected, 30 men and 64 women: 72 patients treated with zoledronate, 16 with alendronate, 4 with neridronate, and 1 each were given ibandronate and clodronate (Tables 1–3). The suspension of treatment with bisphosphonates was dictated not by the presence of BRONJ, but by the clinical condition of the patient.

The mean (SD) age of the patients was 66 (11) years. A parametric correlation test for sex showed that the age for men was 66 (11) years and for women 64 (11).

Three patients were withdrawn from the study 3, 5, and 6 months after their first visit because of severe pain, and

Table 1
Dosage and duration of treatment with bisphosphonates.

| | Zoledronate (n = 72) | Alendronate (n = 16) | Neridronate (n = 4) | Ibandronate (n = 1) | Clodronate (n = 1) |
|-------------------|----------------------|----------------------|---------------------|---------------------|--------------------|
| Dose (mg) | 4 | 70 | 2 | 2 | 100 |
| Route | IV | Oral | IV or IM | IV | IM |
| Timing | 4-weekly | Weekly | 3-monthly | 3-monthly | 2-weekly |
| Duration (months) | | | | | |
| <6 | 1 | 0 | 0 | 0 | 0 |
| 6–12 | 12 | 2 | 0 | 0 | 0 |
| 12–18 | 26 | 1 | 1 | 0 | 0 |
| 18–24 | 21 | 4 | 0 | 0 | 0 |
| 24+ | 12 | 9 | 3 | 1 | 1 |

IV = intravenous, IM = intramuscular.

Table 2
Duration for which bisphosphonates were suspended.

| | Zoledronate (n = 72) | Alendronate (n = 16) | Neridronate (n = 4) | Ibandronate (n = 1) | Clodronate (n = 1) |
|-------------------|----------------------|----------------------|---------------------|---------------------|--------------------|
| Duration (months) | | | | | |
| None | 39 | 7 | 3 | 1 | 1 |
| <6 | 16 | 6 | 0 | 0 | 0 |
| 6–12 | 5 | 0 | 1 | 0 | 0 |
| 12–18 | 8 | 3 | 0 | 0 | 0 |
| 18–24 | 4 | 0 | 0 | 0 | 0 |

Table 3
Clinical staging. No patients with stage 3 disease were included in the study.

| | Zoledronate (n = 72) | Alendronate (n = 16) | Neridronate (n = 4) | Ibandronate (n = 1) | Clodronate (n = 1) |
|-------|----------------------|----------------------|---------------------|---------------------|--------------------|
| Stage | | | | | |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 0 | 7 | 0 | 1 | 0 |
| 2 | 72 | 9 | 4 | 0 | 1 |

Stage 0: Patients with no clinical evidence of necrotic bone, but non-specific symptoms or clinical and radiographic findings.

Stage 1: Exposed and necrotic bone in patients with no symptoms and with no evidence of infection.

Stage 2: Exposed and necrotic bone in patients with pain and clinical evidence of infection.

were treated by debridement. Ninety-one patients developed bony sequestra (the endpoint) and were operated on (19 under general, and 72 under local, anaesthesia) within 15 months. The Kaplan–Meier analysis showed that the mean time to formation of bony sequestra was 8 months (range 5–11). The results of the Mantel–Haenszel (log-rank) test for the descriptive statistical analysis are shown in Fig. 1. The difference

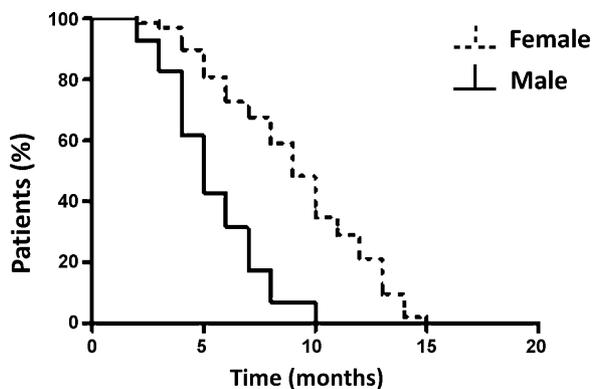


Fig. 1. Time of formation of bony sequestra in men and women (Kaplan–Meier curve).

between the mean (SD) time to develop sequestra in men (5 (range 2–8) months) and women (9 (range 6–12) months) was highly significant ($p < 0.0001$).

Histological analysis of the bony sequestra showed areas characterised by the predominance of bony structures with wide, acellular, necrotic sequestra and large, scalloped Haversian canals that contained inflammatory cells.

During the 6-month postoperative follow-up period no complications were reported. After 6 months, complete healing of the soft tissues was noted in all patients, with no signs of inflammation or exposed bone. The panoramic radiographs taken after 6 months postoperatively showed no signs of new formation of BRONJ (Figs. 2 and 3).

The three patients who were withdrawn from the study all had signs of recurrence of the disease, with exposure of necrotic bone.

Discussion

BRONJ was first described by Marx, and Ruggiero et al., who recognised that the aetiology involved both local and systemic factors.^{5,6} Exposure to zoledronate (in the setting



Fig. 2. Preoperative panoramic radiograph showing a bony sequestrum.

of managing malignancy) remains the main risk factor for BRONJ, with a cumulative incidence ranging from 0.8% to 12%.^{2,4}

The AAOMS guidelines emphasise the importance of prevention of BRONJ before giving bisphosphonates. Indeed, the elimination of all infective foci and trauma before treatment is started can almost entirely eliminate the risk of BRONJ.^{1,2}

The patients with BRONJ respond less predictably to the established treatment of non-bisphosphonate-related osteomyelitis or osteoradionecrosis, and the effectiveness of debridement of the osteonecrotic lesion is variable. It may be difficult to obtain a surgical margin with viable bone, and then completely remove the necrotic bone. Support with antibiotics and local antiseptics was therefore suggested.² When pharmacological treatments are not able to control the development of the complications of BRONJ, clinicians should undertake radical treatments such as resection of the bone involved.^{2,7} Debridement is, therefore, palliative care awaiting resection.⁸

McLeod et al.,⁹ in a review, categorised several strategies: conservative treatment, non-surgical treatment, surgical treatment (local or radical intervention), and adjunctive measures. The conservative approach consists of antiseptic



Fig. 3. Postoperative panoramic radiograph 6 months after removal of a bony sequestrum.

mouth washes and analgesics, the aim of which is to reduce the risk of infection of the exposed bone and it is indicated for patients with exposed bone but no signs of infection (stage 1).^{2,9} A non-surgical approach is advised for patients with exposed bone but signs of infection and inflammation (stage 2). This treatment, described in the AAOMS guidelines, consists of antimicrobials (amoxicillin, clindamycin, and metronidazole) and antifungals, in addition to mouth washes and analgesia.^{2,9} Recently, some authors have reported the beneficial effect of low-level laser therapy to reduce the BRONJ-related pain and inflammation.^{10,11} McLeod et al. distinguished between two different approaches: local and radical intervention. The most common approach is the simple removal of the bony sequestrum, without raising mucoperiosteal flaps and exposing the adjacent bone.⁹ A conservative surgical approach has less stress for patients and, from our results, may not result in recurrences. This is because the margins of necrotic bone are well-defined.

Surgical treatment is not delayed in patients with serious pain that is refractory to pharmacological treatment, according to the AAOMS guidelines, nor is it delayed in patients with fractures or at risk of mandibular fracture whether or not a sequestrum has developed. We saw no case of fracture or extension of necrotic lesions to the inferior border of the mandible, probably because pharmacological treatment may minimise the progression of the necrotic area.² Bagan et al. compared BRONJ with osteoradionecrosis, and reported that fractures of the jaw and skin fistulas were more likely after osteoradionecrosis.¹²

Guidelines about the discontinuation of bisphosphonates state that, in patients taking them intravenously, long-term discontinuation may be beneficial in established sites of BRONJ, to reduce clinical symptoms and the risk of development of a new site of osteonecrosis.² According to work published by Migliorati et al., the suspension of treatment is essential, even if there is no immediate clinical improvement.¹³ However, some authors think that temporary discontinuation of drugs does not alter the clinical course of disease.¹⁴

We have found that the patients who were given zoledronate during the support phase took longer to form a bony sequestrum than patients whose treatment was suspended and patients treated with other bisphosphonates. Twenty-six of 30 men had no zoledronate during treatment, and the last women to develop a sequestrum, had not stopped treatment with zoledronate. However, we did not recommend the discontinuation of bisphosphonates because, according to some authors, the patient may develop systemic complications such as recurrences of pain, progression of osteolytic lesions, or bony metastases.¹⁴ The suspension of bisphosphonates was not dictated by the presence of BRONJ, but by the condition of each patient. We found no correlation between the duration of treatment with bisphosphonates and the formation of bony sequestra. We also found that patients taking zoledronate complained of increased pain and exacerbation

of the inflammation during the days after the injection of zoledronate.

We are aware of the limitations of the design of the present study. The sample of patients is not large, and it is not a controlled study. Consequently, it ranks low in the hierarchy of ideal evidence. We did not use a control group for ethical reasons: debridement is not a safe approach, and may induce postoperative recurrences that require the patient to have further debridements.

The results of our case series are promising, however, because BRONJ did not recur in any of our patients. The three patients withdrawn from the study who were treated by debridement developed recurrences of BRONJ. The prevention of infection by the maintenance of good oral hygiene and suitable drugs (mouth rinses, antibiotics, anti-inflammatories, and analgesics) reduced infection and pain and therefore allowed enough time for the formation of bony sequestra, after a mean (SD) of 8 (3) months (5 (3) months in men and 9 (3) in women).

Several different definitions have been used for a bony sequestrum in other publications. According to a pathological definition, it is defined as a piece of devitalised bone that has separated from the surrounding bone during the process of necrosis. According to this definition, infected bone is the main condition that may present with a sequestrum.¹⁵ The physiopathological evolution of BRONJ to a bony sequestrum allowed us to delay the intervention, and to avoid an aggressive procedure, which might have resulted in recurrence because of the difficulty of obtaining a surgical margin with healthy bleeding bone.

At present, panoramic radiography is the primary imaging choice followed by CT, which is a powerful tool for identifying the margins of a sequestrum. The presence and dimensions of a sequestrum, its proximity to important anatomical structures and its margins, were clearly defined whenever the lesion was seen on CT. When we have accurate information about the margins of the sequestrum, we may remove it without trauma to the adjacent alveolar bone.¹⁶

Within the limits of this study, we conclude that by waiting for a bony sequestrum to form it is possible, by controlling infection and pain, to use a conservative surgical approach, except in cases of severe pain or if there is a risk of fractures. This non-aggressive approach makes it possible to remove all necrotic bone, avoid damage to the adjacent healthy bone, and avoid recurrences.

References

1. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 2007;**65**:369–76.
2. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehotra B. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws – 2009 update. *J Oral Maxillofac Surg* 2009;**67**(5 Suppl.):2–12.
3. Ruggiero SL, Carlson ER, Assael LA. Comprehensive review of bisphosphonate therapy: implications for the oral and maxillofacial surgery patient. *J Oral Maxillofac Surg* 2009;**67**(5 Suppl.):1.
4. Sedghizadeh PP, Stanley K, Caligiuri M, Hofkes S, Lowry B, Shuler CF. Oral bisphosphonate use and the prevalence of osteonecrosis of the jaw: an institutional inquiry. *J Am Dent Assoc* 2009;**140**:61–6.
5. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003;**61**:1115–7.
6. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004;**62**:527–34.
7. Carlson ER, Basile JD. The role of surgical resection in the management of bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofacial Surg* 2009;**67**(5 Suppl.):85–95.
8. Vescovi P, Nammour S. Bisphosphonates-related osteonecrosis of the jaw (BRONJ) therapy. A critical review. *Minerva Stomatol* 2010;**59**:181–213.
9. McLeod NM, Patel V, Kusanale A, Rogers SN, Brennan PA. Bisphosphonate osteonecrosis of the jaw: a literature review of UK policies versus international policies on the management of bisphosphonate osteonecrosis of the jaw. *Br J Oral Maxillofac Surg* 2011;**49**:335–42.
10. Romeo U, Galanakis A, Marias C, et al. Observation of pain control in patients with bisphosphonate-induced osteonecrosis using low level laser therapy: preliminary results. *Photomed Laser Surg* 2011;**29**:447–52.
11. Vescovi P, Merigo E, Manfredi M, et al. Surgical treatment of maxillary osteonecrosis due to bisphosphonates using an Er:YAG (2940 nm) laser discussion of 17 clinical cases (in French). *Rev Belge Med Dent (1984)* 2009;**64**:87–95.
12. Bagan JV, Jiménez Y, Hernández S, et al. Osteonecrosis of the jaws by intravenous bisphosphonates and osteoradionecrosis: a comparative study. *Med Oral Patol Oral Cir Bucal* 2009;**14**:e616–9.
13. Migliorati CA, Schubert MM, Peterson DE, Seneda LM. Bisphosphonate associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy. *Cancer* 2005;**104**:83–93.
14. Gallego L, Junquera L. Consequence of therapy discontinuation in bisphosphonate-associated osteonecrosis of the jaws. *Br J Oral Maxillofacial Surg* 2009;**47**:67–8.
15. Jennin F, Bousson V, Parlier C, Jomaah N, Khanine V, Laredo JD. Bony sequestrum: a radiologic review. *Skeletal Radiol* 2011;**40**:963–75.
16. Elad S, Gomori MJ, Ben-Ami N, et al. Bisphosphonate-related osteonecrosis of the jaw: clinical correlations with computerized tomography presentation. *Clin Oral Investig* 2010;**14**:43–50.