Osteonecrosis of the Jaw and Nonmalignant Disease: Is There an Association with Rheumatoid Arthritis?

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ABSTRACT. ***Objective.*** To review cases of bisphosphonate-related osteonecrosis of the jaw (BRONJ) occurring in association with benign disease and to describe and compare the clinical course and outcome for patients with BRONJ and rheumatoid arthritis (RA) or osteoporosis.

Methods. We retrospectively reviewed observations of all patients referred for treatment and followup for BRONJ from January 2007 to December 2011. Only patients with malignant disease were excluded. Demographic data, medical history, maxillofacial findings, BRONJ treatment, and followup were reviewed for each case.

Results. Over a 5-year period, we diagnosed 112 patients with BRONJ. Among these patients, 15 received bisphosphonate (BP) treatment for nonmalignant disease (mean age 65.7 ± 19.8 yrs, 80% women). Patients received BP for a variety of reasons: 8 (53%) to prevent osteoporosis in association with underlying RA; 6 (40%) to prevent idiopathic osteoporosis; and 1 (7%) to treat ankle algodystrophy. The mean oral BP exposure period was 48.4 months (median 36 mo). In 13 cases (86.6%), BRONJ was diagnosed following dental extraction. Of the 8 patients with RA, 5 (62.5%) were taking prednisone at the time of the discovery of BRONJ. Major surgery, sequestrectomy, or alveolectomy was performed in 9 patients (60%), all of whom healed within 3 to 36 months (mean 11.5 mo). Comparative analysis of all the variables showed no statistically significant differences between patients with RA and others.

Conclusion. ONJ is a rare adverse effect of BP therapy, especially when administered orally. Within the limits of our study, we were unable to demonstrate a difference in BRONJ disease spectrum, clinical course, or outcome between patients with and those without RA. (J Rheumatol First Release March 15 2013; doi:10.3899/jrheum.120810)

Key Indexing Terms:
OSTEONECROSIS JAW BISPHOSPHONATE
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Bisphosphonates (BP) are powerful bone loss inhibitors. They are used for the symptomatic treatment of malignant osteolytic bone disease (e.g., multiple myeloma and bone metastasis), as well as bone diseases associated with high bone resorption (e.g., postmenopausal osteoporosis, cortisone-induced osteoporosis, or Paget disease)[1].

Data show that a rare but serious adverse effect of BP therapy is osteonecrosis of the jaw (ONJ). BP-related ONJ (BRONJ) is more common among cancer patients receiving intravenous BP (IV-BP) than among patients with nonmalignant disease receiving oral BP (O-BP)[2]. The prevalence of osteonecrosis in patients receiving IV-BP varies from 1% to 12%, depending on the series. Risk factors (e.g., chronic IV-BP therapy, invasive dental procedures, con-

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comitant cancer, select comorbidities) and BRONJ prevention methods seem well established[3].

In contrast, epidemiological, pathophysiological, and clinical data about BRONJ in nonmalignant disease remain scant. The prevalence reported in various series ranges from 1 per 20,000 to 1 per 110,000 patients per year of treatment[4]. BRONJ associated to O-BP (O-BRONJ) has been reported in several small case series and case reports[5,6,7,8], and 200 BRONJ cases associated with osteoporosis have been reported to date[9]. A recent review of literature published between January 2003 and September 2011 found 28 cases of ONJ in patients with rheumatoid arthritis (RA)[10]. In spite of these publications, little evidence exists regarding the strength of the association between BRONJ and BP therapies in nonmalignant disease or related risk factors. Given the increasing number of persons receiving chronic O-BP therapy (sales in France increased 14.7% between 1999 and 2009[11]), it is important to accurately identify pathogenesis, risk factors, and management strategies for BRONJ in patients with nonmalignant disease. Another question of interest is how nonmalignant disease affects the emergence, progression, and effectiveness of osteonecrosis treatment. Indeed, some diseases, such as RA[12], are known to impair oral health.

Our primary objective was to review all cases of nonmalignant BRONJ referred to our dentistry and maxillofacial surgery departments between January 2007 and December 2011. We sought to examine the clinical spectrum, treatment, and followup, as well as potential risk factors associated with the development of the disease. Our secondary objective was to compare BRONJ clinical features, treatment, and followup between patients with RA and patients with other nonmalignant disease.

MATERIALS AND METHODS

Patients. We retrospectively reviewed dental and medical records for patients treated and followed for BRONJ between January 2007 and December 2011 at the dentistry and maxillofacial surgery departments of Hôpital Pitié-Salpêtrière in Paris, France.

Inclusion criteria. We included patients with BRONJ who were treated with BP for nonmalignant disease in the rheumatology or internal medicine clinic.

A BRONJ diagnosis was established based on the American Association of Oral and Maxillofacial Surgeons (AAOMS) criteria[13]: current or previous BP therapy, exposure of bone in the oral-maxillofacial region for > 8 weeks, and no history of radiotherapy to the oral-maxillofacial region.

The diagnosis of BRONJ was adjudicated by 3 authors (2 oral surgeons and 1 maxillofacial surgeon) and adjudication required that all AAOMS diagnostic criteria be met.

Exclusion criteria. Patients with malignant disease and those who were not regularly monitored for their rheumatic disease were excluded.

Medical and epidemiological data. Medical and dental records were reviewed for each patient to obtain data points for sex, age, type of BP used, initial therapeutic indication, comorbidities, other past or current drug treatments, and time-to-onset and detection of BRONJ (spontaneous, following trauma, or dental surgery). Also abstracted from records were anatomic location, stage (AAOMS classification; Table 1), signs of clinical progression, radiological signs, BRONJ histological results, and treatment. Outcome variables included BRONJ healing status and disease duration. Healing status was categorized as healed if there was complete mucosal coverage without exposed bone.

Table 1. Staging of bisphosphonate-related osteonecrosis of the jaw according to guidelines of the American Association of Oral and Maxillofacial Surgeons[12,13].

At-risk category	No apparent exposed/necrotic bone in patients who have been treated with either oral or intravenous bisphosphonates
Stage 0	Nonspecific clinical findings and symptoms such as jaw pain or osteosclerosis but no clinical evidence of exposed bone
Stage 1	Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone, with or without purulent drainage
Stage 3	Exposed/necrotic bone in patients with pain, infection, and 1 or more of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border or sinus floor

Statistical analysis. The chi-square test was used to compare patient characteristics such as sex and trigger event. Student's t test was used to compare the treatment duration and BP treatment of the 2 groups of patients. The level of significance was fixed at $p < 0.05$. The statistical analysis was done with GraphPad Prism 5.

RESULTS

Between 2007 and 2011, we found 112 cases of BRONJ, 97 of which occurred in patients with malignant disease. A total of 15 patients with BRONJ received BP therapy for benign disease: 8 (53%) for RA, 6 (40%) for idiopathic osteoporosis, and 1 (7%) for ankle algodystrophy. The sample included 12 women and 3 men with a mean age of 65.7 ± 19.8 years (range 39 to 89 yrs; Table 2). Of the 15 patients, 13 received O-BP therapy daily or weekly. BP used included ibandronate (3 patients), risedronate (4 patients), and alendronate (8 patients), over a mean exposure period of 48.4 months (range 6 to 108 mo), for an average cumulative dose of 4050 mg, 5340 mg, and 16,600 mg, respectively (Table 2). Three of the 15 patients received > 1 BP. The rationale for oral BP treatment for patients with RA was prevention of osteoporosis associated with RA or corticosteroid-induced osteoporosis.

Two patients received zoledronate-based IV-BP therapy. One patient was started on pamidronate, then switched to zoledronate. BP were administered for 1 patient with a history of ankle algodystrophy (Table 2). For IV-BP therapy, ONJ was diagnosed 22 months after treatment initiation (Table 2).

All patients were nonsmokers and 1 patient had documented diabetes mellitus. Of the 8 patients with RA, relevant comorbidities include 1 case of Sjögren syndrome

Table 2. Patient characteristics (n = 15). BRONJ was diagnosed following tooth extraction except in Patients 4 and 15, whose diagnoses were spontaneous.

Patient	Age, yrs	Sex	Disease	BRONJ Site	BRONJ Stage	BP	Duration (mo), Cumulative BP Dose, mg	BRONJ Management	Followup, mo	Comorbidity	Therapy
1	51	F	RA	R, L mandibles	2	Risedronate	24, 3360	Medical*	No	SS	MTX
2	59	F	RA	Mandible	2	Risedronate	60, 8400	Medical, surgical	Healing, 24	HTN	LEF, prednisone, fluindione
3	56	M	RA	L, mandible	2	Zoledronate, pamidronate	36, 48 12, 18	Medical	Healing, 6	Arrhythmias	Fluindione, bisoprolol, prednisone
4	57	F	RA	R maxilla	1	Alendronate	96, 26,880	Medical, surgical	Healing, 3	None	Adalimumab
5	39	M	RA	R, L mandibles	2	Alendronate	36, 10,080	Medical, surgical	No	Renal failure	HCQ, MTX, prednisone
6	82	F	RA	Mandibular fracture	3	Alendronate, ibandronate	12, 180 18, 270	Medical, surgical	Healing, 13	CAD	Ramipril, clopidogrel, furosemide, atenolol, prednisone
7	84	F	RA	Maxillary sinus	3	Ibandronate	36, 5400	Medical, surgical	Healing, 24	None	Prednisone, MTX
8	89	F	RA	R maxilla	2	Alendronate	60, 16,800	Medical	Healing, 5	None	Prednisone
9	78	F	OP	L mandible	2	Risedronate	36, 5400	Medical, surgical	Healing, 6	None	None
10	80	M	OP	L mandible	2	Ibandronate	18, 2700	Medical, surgical	Healing, 36	Diabetes	Metformin
11	79	F	OP	R mandible	2	Alendronate	48, 13,400	Medical, surgical	Healing, 3	None	None
12	89	F	OP	R maxilla	2	Alendronate	84, 23,520	Medical, surgical	Healing, 12	None	None
13	70	F	OP	L maxilla	2	Alendronate, risedronate	36, 10.080 72, 10,800	Medical	Healing, 8	None	None
14	69	F	OP	L maxilla	2	Alendronate	36, 10,080	Medical	Healing, 4	None	None
15	64	F	AD	Dental implant, R mandible	2	Zoledronate	6, 5	Medical, surgical	Healing, 6	None	Diclofenac

* Medical treatment: oral rinse and oral antibiotics (amoxicillin 1 g plus clavulanic acid 125 mg po twice daily or clindamycin 600 mg po plus metronidazole 500 mg po twice daily). BRONJ: bisphosphonate-related osteonecrosis of the jaw; BP: bisphosphonate; RA: rheumatoid arthritis; SS: Sjögren syndrome; MTX: methotrexate; HTN: hypertension; LEF: leflunomide; HCQ: hydroxychloroquine; CAD: coronary artery disease; OP: osteoporosis; AD: algodystrophy.

and 1 case of renal insufficiency. Five patients (62.5%) were receiving glucocorticoid therapy and 5 were receiving disease-modifying antirheumatic medications (DMARD; Table 2).

In 13 patients (86.6%), BRONJ was diagnosed following dental extraction (Table 2). There were 2 cases of spontaneous ONJ. One case of ONJ occurred at the site of 2 mandibular dental implants placed 15 days prior to the first zoledronate injection, whereas the second case appeared at the site of a maxillary first molar in a female patient with RA who had been receiving alendronate therapy for the previous 96 months (Table 2).

AAOMS BRONJ stages for these 15 patients were as follows: stage 1, 1 patient (6.7%); stage 2, 12 patients (80%); and stage 3, 2 patients (13.3%; Tables 1 and 2)[12]. BRONJ lesions were localized to the mandibular premolars in 6 patients (bilateral mandibular for 2 patients), the maxillary molars in 6 patients, and the mandibular incisors in 1 patient. At the initial patient visit, 13 patients exhibited jawbone exposure, pain, and purulent discharge (Table 2). Panoramic radiographs were available for all patients and showed mixed radiolucent and radio-opaque lesions consistent with osteonecrosis for all BRONJ stages except stage 1. Forty percent of radiographs showed persistent tooth sockets following extractions. In stages 2 and 3, osteonecrosis appeared as an irregular area of osteosclerosis with a cotton-wool-like appearance. Moreover, osteolysis with a central portion of separated bone was present in 6 patients. Patients for whom oral surgery was necessary to treat BRONJ underwent pathological investigation of perioperative bone samples, which confirmed osteonecrosis with associated acute, subacute, or chronic inflammatory change, without signs of malignancy.

All patients were treated with antimicrobial oral rinse and oral antibiotics (amoxicillin 1 g plus clavulanic acid 125 mg po twice daily, or clindamycin 600 mg po plus metronidazole 500 mg po twice daily). Major surgery (mandibulectomy in 1 case), sequestrectomy, or alveolectomy was performed in 9 patients (60%). All patients diagnosed with BRONJ in this study discontinued BP therapy.

Thirteen patients were followed for 6 to 40 months; 2 patients did not return to the clinic. Complete healing was achieved in 13 patients in a mean of 11.5 months (range 3 to

36 mo). The 1 patient with diabetes mellitus experienced the longest BRONJ healing time.

Comparative analysis of all variables studied showed no statistically significant difference between BRONJ in patients with RA and BRONJ in those with other nonmalignant disease (Table 3).

DISCUSSION

We have described 15 cases of ONJ associated with BP therapy for nonmalignant disease, including 7 cases of idiopathic osteoporotic patients with BRONJ. BRONJ associated with RA has been reported rarely[10]. BRONJ prevalence in patients with RA is unknown and, to our knowledge, only 28 cases have been described to date. The unique aspect of the current case series is that 8 of 15 patients had RA. These 8 patients constitute the largest cohort of patients with RA-associated BRONJ described to date and, contrary to our expectations, osteonecrosis in patients with RA seemed very similar to osteonecrosis observed in osteoporotic patients. It should be noted that 5/8 patients with RA were taking prednisone at the time of the development of BRONJ.

Table 3. Comparison of clinical BRONJ criteria between patients with rheumatoid arthritis (RA) and those with other nonmalignant disease. Data are n (%) unless otherwise indicated. p values were not significant.

Criteria	RA, n = 8	Others, n = 7
Age, yrs, mean	64.6	75.6
Female	6 (75)	6 (85)
BP, mo, mean	48.8	48
BP administration		
Alendronate	3 (37.5)	3 (42.9)
Risedronate	2 (25)	1 (14.3)
Ibandronate	1 (12.5)	1 (14.3)
Zoledronate	0	1 (14.3)
Zoledronate/pamidronate*	1 (12.5)	0
Alendronate/ibandronate*	1 (12.5)	0
Alendronate/risedronate*	0	1 (14.3)
Steroid		
No	3 (37.5)	7 (100)
Yes	5 (62.5)	0
Trigger event		
Dental extraction	7 (87.5)	6 (85.7)
Spontaneous	1 (12.5)	1 (14.3)
Involved site		
Mandible	5 (62.5)	4 (57.1)
Maxilla	3 (37.5)	3 (42.9)
BRONJ stage		
Stage 1 (%)	12.5	0
Stage 2 (%)	62.5	100
Stage 3 (%)	25	0
BRONJ treatment		
Antibiotics and surgery	5 (62.5)	5 (71.4)
Antibiotics	3 (37.5)	2 (28.6)
Complete healing, mo, mean	12.5	10.7

* Patients received treatment successively. BRONJ: bisphosphonate-related osteonecrosis of the jaw; BP: bisphosphonate.

The large proportion of patients with RA in our study is somewhat surprising. In the French general population, the prevalence of osteoporosis (9.7%)[14] is much greater than the prevalence of RA (0.3%)[15]. However, our large proportion of patients with RA may have resulted from recruitment bias, as these patients have an increased risk of periodontal disease and often require dental care or oral surgery. Additionally, our department is a referral center for the prevention and treatment of osteonecrosis. Unlike other authors, we have considered RA, not as a comorbidity but as a primary disease, even for patients who received BP for RA-induced osteoporosis. Indeed, our original hypothesis was that RA could affect or influence the occurrence, development, or healing of osteonecrosis. First, RA has been associated with periodontal disease and other oral health complications (2 major BRONJ risk factors)[16,17]. Second, recent literature suggests that RA alone could be an additional risk factor for BRONJ[10,16,17,18]. The methods used in our study and others[10,18,19,20] were not intended to identify RA as a risk factor associated with BRONJ, notably because there was no control group.

Mean time-to-onset of BRONJ following O-BP initiation is about 3 years[5]. In 12 of 15 patients, treatment duration was 36 months or more prior to BRONJ diagnosis. The published literature suggests that the minimum mean cumulative dose of O-BP (alendronate or risedronate) needed to cause BRONJ would be 13,870 mg (range 900 to 72,000 mg)[5]. Our patients' experience was consistent with these previously published findings.

Although RA pathophysiology may appear to modify or worsen BRONJ, our study shows that BRONJ clinical, radiological, and histological aspects were very similar, regardless of the presence or absence of RA. Similarly, we were unable to demonstrate a statistically significant difference for time to BRONJ onset (4.1 yrs in patients with RA vs 4 yrs in osteoporotic patients) or treatment course (62.5% of patients with RA undergo surgery vs 71.4% of non-RA patients). Finally, we did not find refractory BRONJ with prolonged healing times in patients with RA (12.5 mo for patients with RA vs 10.7 for the other patients).

A recent study[21] highlighted the effect of comorbidities (e.g., diabetes, systemic inflammatory disease, glucocorticoid therapy, DMARD therapy) on healing of osteonecrosis following oral BP therapy. In contrast to our findings, the most common comorbidity in that study was diabetes (30%), with only 4 patients (13%) affected by RA. Our cohort included only 1 patient with diabetes, for whom the healing time was prolonged (36 mo). This observation suggests that the comorbidity effect reported in the O'Ryan and Lo study[21] was due to diabetes alone, because we could not show any differences in healing time between the RA and osteoporosis groups. However, the sample size for all these studies was much too small to speculate about cause and effect. Both our study and the others must be considered

as preliminary because of their retrospective design and small patient numbers.

Data obtained in our patient series confirm that identifying specific risk factors of BRONJ is particularly difficult for patients receiving BP for nonmalignant disease. Perhaps it would be of more interest to analyze the effect of each comorbidity on BRONJ (vs comparing diabetes comorbidity with RA comorbidity, as our study suggests). This would be extremely difficult, given the small numbers of affected patients (we would be subdividing an already small and underpowered sample size). Lastly, it has been difficult to evaluate the potential role of steroids and specific DMARD (methotrexate, leflunomide, or hydroxychloroquine) because only patients with RA (not patients with osteoporosis) received these medications.

However, corticosteroid use may be a risk factor. Our results show that 5 of 15 patients (33.3%) were treated with steroids and that all 5 patients receiving steroids who developed O-BRONJ had RA. This would suggest, within the limits of the size of our cohort, that steroids may have a role in the development of O-BRONJ and in particular in patients with RA.

Some study limitations should be noted. First, as mentioned, our cohort size was small, primarily because of the rarity of BRONJ in nonmalignant disease. A control group (e.g., osteoporotic patients with or without RA and without BP treatment) is missing; thus identification of risk factors is not possible. Another study bias is that patients were referred to our department for ONJ. Our study could have been more powerful if patients were followed prospectively from BP initiation; however, the rarity of the outcome precludes this type of study design.

The main pathophysiological hypotheses proposed to explain onset of BRONJ are decline in bone remodeling (loss of homeostasis in bone formation and resorption balance)[22,23], inhibition of capillary neoangiogenesis[24], and endothelial proliferation aggravating ischemic damage[25]. Recent findings suggest that RA is an additional risk factor for BRONJ[10,18,19,20] because of associated immunodepression, the effect on angiogenesis, and increased risk of bacterial infection[26]. Despite the literature review and our hypothesis, our analysis did not show differences between BRONJ in patients with osteoporosis and those with osteoporosis and RA. These results are particularly intriguing because of the pathophysiology of RA itself and its effects on oral health. The only difference between the 2 groups of patients is that 62.5% of patients with RA were taking steroids. RA in association with steroid seems to be particularly important in the pathophysiology of BRONJ and requires further study.

Although few cases of O-BRONJ have been reported, all current recommendations suggest a preventive and prophylactic approach to minimize disease development. It has been shown that implementing preventive measures leads to decreased ONJ cases among oncology patients[27]. These preventive measures help reduce the need for dental-alveolar surgery and bone surgery, which are major risk factors for BRONJ (BRONJ risk increases from 37% to 70% in oncology patients receiving IV-BP)[28,29]. There are few data currently available to confirm this risk in patients receiving O-BP therapy. Some studies have demonstrated that placing dental implants in patients receiving O-BP does not increase treatment failure in control populations[30], despite a number of case reports describing BRONJ at implant sites[31,32]. However, our finding that nearly 90% of our patients experienced stage 2 BRONJ prompts us to agree with Ruggiero[3] that rheumatologists and dentists should collaborate to create earlier, improved BRONJ prevention and detection strategies.

Our study is the first, to our knowledge, to distinguish and compare 2 groups of patients treated with BP for nonmalignant disease. Within the limits of our study, our results suggest that RA does not alter the clinicopathological features of BRONJ or treatment. Further studies are needed to assess the incidence and prevalence of osteonecrosis in patients with RA.

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