Osteonecrosis of the jaws and non-malignant disease

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Introduction

Bisphosphonates (BP) are powerful bone resorption 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). However, recent data showed that a rare, but serious, adverse effect of BP therapy is bisphosphonate related osteonecrosis of the jaw (BRONJ). Given the increasing number of persons receiving chronic oral-BP therapy, it is important to accurately identify pathogenesis, risk factors and management strategies for BRONJ in patients with non-malignant disease. The objective of this study was to review cases of BRONJ occurring in association with benign disease and to describe and compare the clinical course and outcome for patients with BRONJ and rheumatoid arthritis or osteoporosis.

We retrospectively reviewed observations of all patients referred for treatment and follow-up for BRONJ from January 2007 to December 2011. Demographic data, medical history, maxillofacial findings, BRONJ treatment and follow-up were reviewed for each case. Over a five-year period, we diagnosed 112 patients with BRONJ. Among these patients, 15 received bisphosphonate treatment for non-malignant disease.

Patient	Age (years)	Sex	Disease	Trigerevent	BRONJ site	BRONJ stage	Bisphosphonate	Duration (mo) Cumulative dose (mg)	BRONJ management	Followup (mo)	Comorbidities
1	51	F	Rheumatoid arthritis	Tooth extraction	Right and left mandibles	2	Risedronate	**24** *3360*	Medical	Not controlled	Sjogren's Syndrome Methotrexate
2	59	F	Rheumatoid arthritis	Tooth extraction	Mandible	2	Risedronate	**60** *8400*	Medical Surgery	Complete healing (24)	Hypertension Phlebitis Leflunomide Prednisone Fluindione
3	56	M	Rheumatoid arthritis	Tooth extraction	Left mandible	2	Zoledronate Pamidronate	**36** *48* **12** *180*	Medical	Complete healing (6)	Arrhythmias Fluindione Bisoprolol Prednisone
4	57	F	Rheumatoid arthritis	Spontaneous	Right maxillar	1	Alendronate	**96** *26880*	Medical Surgery	Complete healing (3)	Adalimumab
5	39	M	Rheumatoid arthritis	Tooth extraction	Right and left mandibles	2	Alendronate	**36** *10080*	Medical surgery	Not controlled	RenalInsufficiency Hydroxychloroquine Methotrexate Prednisone
6	82	F	Rheumatoid arthritis	Tooth extraction	Mandibular fracture	3	Alendronate Ibandronate	**12** *280* **18** *2700*	Medical Surgery	Complete healing (13)	Angor pontage coronarien stent triatec plavix vastarel lasilix tenormine lipanthyl cortancyl
7	84	F	Rheumatoid arthritis	Tooth extraction	Maxillar sinus	3	Ibandronate	36 *5400*	Medical Surgery	Complete healing (24)	Prednisone Methotrexate
8	89	F	Rheumatoid arthritis	Tooth extraction	Right maxillar	2	Alendronate	60 *16800*	Medical	Complete healing (5)	Prednisone
9	78	F	Osteoporosis	Tooth extraction	Left mandible	2	Risedronate	36 5400	Medical Surgery	Complete healing (6)	None
10	80	M	Osteoporosis	Tooth extraction	Left mandible	2	Ibandronate	18 2700	Medical Surgery	Complete healing (36)	Diabetes Parkinson disease Metformine
11	79	F	Osteoporosis	Tooth extraction	Right mandible	2	Alendronate	48 13400	Medical Surgery	Complete healing (3)	None
12	89	F	Osteoporosis	Tooth extraction	Right maxillar	2	Alendronate	84 *23520*	Medical Surgery	Complete healing (12)	None
13	70	F	Osteoporosis	Tooth extraction	Left maxillar	2	Alendronate Risedronate	**36** *10080* **72** *10800*	Medical	Complete healing (8)	None
14	69	F	Osteoporosis	Tooth extraction	Left maxillar	2	Alendronate	36 *10080*	Medical	Complete healing (4)	None
15	64	F	Algodystrophy	Spontaneous	dental implant right mandible	2	Zoledronate	6 *5*	Medical Surgery	Complete healing (6)	Diclofenac omeprazole

Table 1: Patient characteristics (n = 15). BRONJ was diagnosed following tooth extraction except in Patients 4 and 15, whose diagnoses were spontaneous.
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.

At risk category	No apparent exposed/necrotic bone in patients who have been treated with either oral or IV 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 one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border or sinus floor

Table 2: BRONJ patients were characterized according to the the AAMOS guidelines (Ruggeriro SL, 2009)

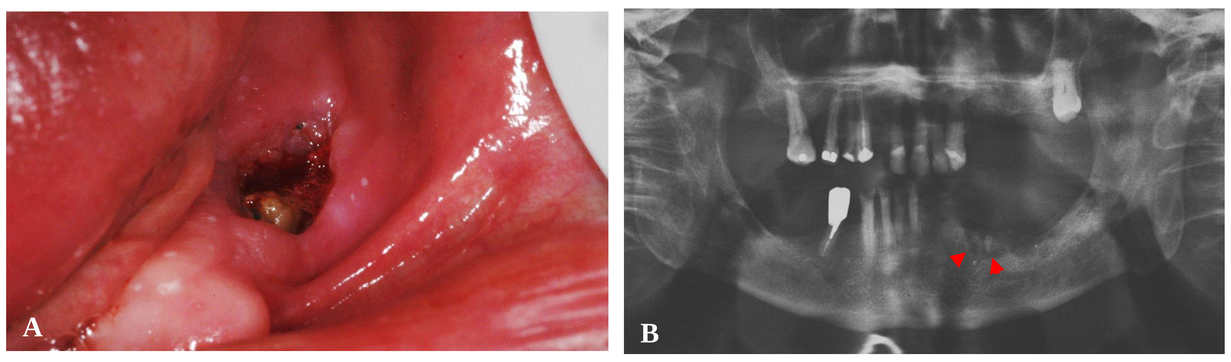

Figure 1: Typical stage 2 BRONJ. A. Clinical photograph showing exposed bone following a tooth extraction. B. Panoramic X-ray showing the lost of mandibular bone and the characteristic radioluscent and radio opaque lesion (red arrow heads).

Criteria	RA (n=8)	Others (n=7)	*p*
Age (mean, years)	64.63	75.57	*ns*
Female (%)	75 %	85%	*ns*
BP duration (mean, months)	48.75	48	*ns*
Glucocorticoids	75 %	0%	
DMARDs	65.2%	0%	
Alendronate (mean, mg)	13510	14270	*ns*
Trigger event (extraction)	87.5%	85.7%	*ns*
BRONJ stage			
Stage 1 (%)	12.5%	0%	*ns*
Stage 2 (%)	62.5%	100%	*ns*
Stage 3 (%)	25%	0%	*ns*
Surgery	62.5%	71.4%	*ns*
Complete healing (mean, months)	12.5	10.71	*ns*

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. DMARDs, disease-modifying antirheumatic drugs : methotrexate, leflunomide, adalimumab, hydroxychloroquine,

Conclusion

Comparative analysis of all the variables showed no statistically significant differences between patients with rheumatoid arthritis and others. However, our study is the first, to our knowledge, to distinguish and compare 2 groups of patients treated with BP for non malignant disease. In conclusion, within the limits of our study (small size cohort, lack of control group, patients referred to our department for ONJ), our results suggest that RA does not alter the BRONJ disease spectrum, clinical course or outcome. Further studies are needed to assess the incidence and prevalence of osteonecrosis of the jaws in patients with RA.

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