

# Comparison of the Clinical Characteristics of Bisphosphonate-associated Osteonecrosis of the Jaw with Inflammation-associated Osteonecrosis of the Jaw in Patients with Osteoporosis and Benign Diseases

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**Objectives:** Osteonecrosis of the jaw (ONJ) involving the use of bisphosphonates is referred to as bisphosphonate-associated ONJ (BONJ). Inflammation also can cause ONJ and it may be called inflammation-associated ONJ (IONJ). The aim of this study was to compare clinical characteristics between BONJ and IONJ.

**Materials and Methods:** Medical records at the Ajou University Hospital were reviewed using key words "osteonecrosis", "sequestrum", and "dead bone" of the mandible and maxilla. Eighteen patients diagnosed with ONJ were identified from January 2003 to December 2009. Using criteria from the American Association of Oral and Maxillofacial Surgeons, 12 cases were diagnosed as BONJ and six as IONJ. Clinical characteristics and treatment modalities, outcomes of two groups of patients were investigated.

**Results:** Patients of the BONJ group were older than those of IONJ group (median: 76.5 years vs. 60 years). In the BONJ group, mandible was more commonly involved sites and percentage of diabetic patients was higher. Three of 12 (25%) BONJ patients received oral glucocorticoids, while none of the IONJ patients. Ten (83.3%) of the BONJ cases and 2 (33.3%) of the IONJ cases were triggered by dental extractions. Though duration of ONJ treatment was longer in the BONJ group than the IONJ group (6.4±5.2 months vs. 2.9±1.9 months), both groups eventually showed good prognosis.

**Conclusions:** ONJ may occur in the absence of bisphosphonate. BONJ occurred in older patients, and needed longer treatment duration compared to IONJ. Prognosis of ONJ was relatively good.

**Key Words:** Osteonecrosis of the jaw, Bisphosphonates, Inflammation

Bisphosphonates are commonly prescribed medications for the treatment of osteoporosis. Recently, osteonecrosis of the jaw (ONJ) has been identified as an important side effect of bisphosphonate therapy. Bisphosphonate-associated osteonecrosis of the jaw

(BONJ) was first reported in 2003.<sup>1,2</sup> Since that time, much has been written with regard to prevention and management. However, ONJ is not a new disease entity and is not always related to the use of bisphosphonate. Nevertheless, reference to ONJ has become usually synonymous with BONJ.

Osteonecrosis is one of the common degenerative and inflammatory disorders of the human skeleton. It typically presents as a painful condition of the hip. Previously it was assumed that this relatively common disorder rarely occurred in the jaw.<sup>3</sup> However, recently

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necrosis of the jawbone leading to exposure of alveolar bone is not a rare condition anymore. ONJ may result from the use of systemic medications including bisphosphonates, glucocorticoids, radiation, infection (bacteria, virus, and fungus), direct chemical toxicity such as agents used in dental treatment, trauma, as well as idiopathic and other etiologies.<sup>4</sup>

Inflammation resulting from any cause can result in ONJ, and it would be termed inflammation-associated ONJ (IONJ). The definition of IONJ used in this study refers to the exposure of jaw bone with benign inflammation, without a history of bisphosphonate use. The etiological factors and the mechanisms by which bisphosphonates cause ONJ are uncertain, although a number of possibilities have been suggested. To better understand the pathophysiology of ONJ, clinical clues could be the initial step of investigation. With this aim, this study compared the clinical characteristics between patients with BONJ and those with IONJ.

## MATERIALS AND METHODS

From January 2003 to December 2009, the electronic and paper medical record systems of the Ajou University Hospital, Suwon, South Korea, were used to identify patients diagnosed with ONJ. A retrospective chart review was performed using electronic key words of pathology reports “osteonecrosis”, “sequestrum” or “dead bone” of the mandible or maxilla. ONJ was confirmed by reviewing paper-based medical records. This study was approved by the Ajou University Hospital Institutional Review Board (AJIRB-MED-OBS-11-099).

Twenty four cases were identified with the diagnosis of ONJ after confirmation by the agreement of the three endocrinologists and two dentists. Among these cases, six patients were excluded because of a diagnosis of underlying malignant diseases (multiple myeloma or breast cancer). Among the remaining 18 patients, 12 patients had BONJ with a history of

bisphosphonate use and 6 patients were diagnosed with ONJ without a history of bisphosphonate use. Twelve patients classified into with BONJ had osteoporosis. Osteoporosis was defined by the World Health Organization (WHO) criteria with T-score of  $-2.5$  or less on the lumbar spine or proximal femur as a bone mineral density that is 2.5 standard deviations or more below the mean peak bone mass (average of young, healthy adults) as measured by dual energy X-ray absorptiometry. Although bone densitometry was not measured in patients with IONJ, that is 6 patients, they were considered not to have osteoporosis, based on the medical records and X-ray findings.

The diagnosis of BONJ according to the American Association of Oral and Maxillofacial Surgeons (AAOMS)<sup>5</sup> definition requires meeting the following criteria: 1) current/previous treatment with bisphosphonate, 2) exposure of necrotic bone in the maxillofacial area for longer than 8 consecutive weeks and 3) no medical history of radiation therapy to the jaw bones. Patients were diagnosed with IONJ if they met criteria 2) and 3), and presented benign inflammation only. Clinical characteristics obtained for the 18 patients were age, gender, site of ONJ, the existence of co-morbidity, medication history, symptoms, radiologic and pathologic data and dental treatment history. Information about the indication, type, dose, duration and discontinuation of bisphosphonate treatment were obtained from the patients with BONJ.

Student's t-test and Chi-square test were used to compare the two groups. To make up for the small cases, Mann-Whitney U test and Fisher's exact test were also used. All statistical analysis was performed by the SPSS 17 software (SPSS Inc., Chicago, IL, USA). The value of  $P < 0.05$  was regarded as statistically significant.

## RESULTS

### 1. Demographics of Patients with BONJ and IONJ

The median age of the patients with BONJ was 76.5 years, and ranged from 66 to 81 years of age. Eleven of the 12 (91.7%) patients were female. All patients with BONJ received oral bisphosphonates for the treatment of osteoporosis: six (50%) patients received alendronate, three (25%) patients received risedronate and three (25%) patients received both alendronate and risedronate in sequence. Alendronate or risedronate were given orally, 70 mg or 35 mg each, once weekly. The average duration of bisphosphonate treatment was  $3.7 \pm 2.4$  years. The median age of the patients with IONJ was 60 years, and ranged from 19 to 72 years of age. Five (83.3%) IONJ patients were female and one (16.7%) was male. The mandible was more commonly involved than maxilla in patients with BONJ: nine (75%) patients had lesions in the mandible and three (25%) patients had lesions in the maxilla. On the contrary, the maxilla was more commonly involved than the mandible in IONJ: two (33.3%) patients had lesions in the mandible and four (66.7%) patients had lesions in the maxilla. Overall, mean age was significantly older in the patients with BONJ compared to those with IONJ ( $P=0.035$ ). The site of osteonecrosis (mandible vs. maxilla) and the existence of co-morbid

diseases were slightly different between two groups without statistical significance which was verified by Fisher's Exact test (Table 1).

### 2. Estimated Prevalence of BONJ

From January 2003 to December 2009, total number of osteoporotic patients was 9,731 in the Ajou University Hospital. Among them, bisphosphonates were prescribed in 7,876 patients. In twelve patients who were diagnosed as BONJ, three patients had been prescribed oral bisphosphonates from the Ajou University Hospital. Based on data, estimated prevalence of BONJ was 38/100,000 (0.038%).

### 3. Clinical Features

The most common initiating event in the patients with BONJ was tooth extraction. Ten (83.3%) patients had a history of tooth extraction as the apparent initiating event. The other two (16.7%) patients had no identifiable specific triggering event. For the IONJ group, three patients had no specific initiating events, two patients had a history of tooth extraction, and one patient had a history of cyst enucleation. Seven (58.3%) patients in the BONJ group had type 2 diabetes mellitus (DM) and two (33.3%) patients in the IONJ group had type 2 DM. Three (25%) patients in the BONJ group were currently receiving or had previously been treated with glucocorticoid medications due to

**Table 1.** Comparison of demographics between patients with bisphosphonate-associated osteonecrosis of the jaw (BONJ) and inflammation-associated osteonecrosis of the jaw (IONJ)

		BONJ (%) n=12	IONJ (%) n=6	P value
Age (years)	Median	76.5	60	<0.05
	Range	66~81	19~72	
Gender (F:M)		11:1	5:1	NS
Site	Mandible	9 (75%)	2 (33%)	NS
	Maxilla	3 (25%)	4 (67%)	NS
BP exposure (years)		$3.7 \pm 2.4^\dagger$	0	
Diabetes mellitus		7 (58%)	2 (33%)	NS
Glucocorticoid use		3 (25%)	0	NS

BONJ: bisphosphonate-associated osteonecrosis of the jaw; IONJ: inflammation-associated osteonecrosis of the jaw; BP: bisphosphonate, NS: not significant.

<sup>†</sup>mean $\pm$ standard deviation

**Table 2.** Clinical characteristics of patients with bisphosphonate-associated osteonecrosis of the jaw (BONJ) and inflammation-associated osteonecrosis of the jaw (IONJ)

	Age/Sex	Underlying diseases	Bisphosphonates (years)	Co-morbid diseases	Co-medications	Initiating events
<b>Bisphosphonate-associated osteonecrosis of the jaw</b>						
1	66/F	Osteoporosis	Alendronate (4)	DM	–	Extraction
2	69/F	Osteoporosis	Alendronate (4)	DM	–	Extraction
3	71/F	Osteoporosis	Alendronate → Risedronate (3)	DM	–	Spontaneous
4	74/F	Osteoporosis	Alendronate (5)	DM	–	Extraction
5	74/F	Osteoporosis	Alendronate (5)	–	–	Extraction
6	76/F	Osteoporosis	Risedronate → Alendronate (1.5)	DM	–	Spontaneous
7	77/F	Osteoporosis	Alendronate → Risedronate (1.5)	–	–	Extraction
8	79/F	Osteoporosis	Risedronate (3)	–	–	Extraction
9	79/F	Osteoporosis	Risedronate (3)	DM, RA	Methyl-prednisolone	Extraction
10	80/F	Osteoporosis	Alendronate (1)	–	–	Extraction
11	80/F	Osteoporosis	Risedronate (7)	DM, RA, IPF	Prednisolone	Extraction
12	81/M	Osteoporosis	Alendronate (3.8)	CRF, CHF	Prednisolone	Extraction, Implant
<b>Inflammation-associated osteonecrosis of the jaw</b>						
13	19/M	Odontogenic cyst	–	–	–	Cyst enucleation
14	49/F	Periodontitis	–	–	–	Spontaneous
15	58/F	Periodontitis	–	–	–	Extraction
16	62/F	Periodontitis	–	–	–	Extraction
17	63/F	Periodontitis	–	DM	–	Spontaneous
18	72/F	Oro-antral fistula	–	DM	–	Spontaneous

BONJ: bisphosphonate-associated osteonecrosis of the jaw; IONJ: inflammation-associated osteonecrosis of the jaw; DM: diabetes mellitus; RA: rheumatoid arthritis; IPF: idiopathic pulmonary fibrosis; CRF: chronic renal failure; CHF: congestive heart failure.

rheumatoid arthritis or cardio-pulmonary diseases. None of the six patients in the IONJ group had a history of glucocorticoid use. According to AAOMS staging for ONJ, one patient from each group were stage 3, and others were stage 2 (Table 2).

#### 4. Treatments and Outcomes

All 18 patients were treated with systemic antibiotics including oral or intravenous antibiotics. All BONJ patients were managed with discontinuation of oral bisphosphonates. Nine (75%) patients in the BONJ group were required surgical intervention including debridement, curettage, saucerization, and sequestrectomy. The other three patients (25%) in the BONJ group were managed with medical treatment without surgical intervention. All patients of the IONJ group were required surgical intervention (Table 3). The mean  $\pm$  standard deviation of treatment duration was  $6.4 \pm 5.2$

**Table 3.** Treatment modalities and types of surgical treatments

Surgical treatments	
<b>Bisphosphonate-associated osteonecrosis of the jaw</b>	
1	Extra-oral fistulectomy, sequestrectomy
2	Debridement, sequestrectomy
3	Bridge cutting
4	Saucerization
5	Debridement, saucerization & sequestrectomy
6	Debridement
7	Conservative care
8	Debridement, saucerization & sequestrectomy
9	Conservative care
10	Debridement, saucerization & sequestrectomy
11	Conservative care
12	Curettage & sequestrectomy and decortification
<b>Inflammation-associated osteonecrosis of the jaw</b>	
13	Debridement
14	Curettage
15	Debridement
16	Sequestrectomy
17	Sequestrectomy
18	Advanced flap, debridement

**Table 4.** Comparison of treatment modalities and duration, and prognosis of bisphosphonate-associated osteonecrosis of the jaw (BONJ) and inflammation-associated osteonecrosis of the jaw (IONJ)

	BONJ (%) n=12	IONJ (%) n=6	P value
Treatment modality			
Surgical intervention	9 (75%)	6 (100%)	NS
Medical treatment			
Discontinuation of bisphosphonate	12 (100%)	(-)	
Antibiotics treatment	12 (100%)	6 (100%)	
Duration of treatment (months)	6.4±5.2	2.9±1.9	<0.05
Prognosis			
Recovery	11 (92%) <sup>†</sup>	6 (100%)	NS

BONJ: bisphosphonate-associated osteonecrosis of the jaw; IONJ: inflammation-associated osteonecrosis of the jaw; NS: not significant

<sup>†</sup>One patient died of myocardial infarction, which was not related to BONJ.

months for the BONJ patients and 2.9±1.9 months for the IONJ patients (*P*<0.05). This difference with treatment duration did not change after adjustment of subjects' age.

In the BONJ group, complete healing was achieved in eleven (92%) patients; one patient died of a myocardial infarction, which was not related to BONJ. All six patients with IONJ achieved complete resolution (Table 4).

## DISCUSSION

As far as we know, this is the first study to compare clinical characteristics and treatment outcomes of patients with BONJ and those with IONJ. In the current study, patients of the BONJ group were older. In the BONJ group, a mandible was more commonly involved site than a maxilla. The percentage of steroid users and patients with DM was higher, and most cases were triggered by dental extractions in BONJ group. Though duration of ONJ treatment was longer in the BONJ group than the IONJ group, both groups eventually showed good prognosis.

The results of this study have similarities with previous studies as follows.

The estimated incidence of BONJ in patients treated with intravenous bisphosphonates is 4.5~12.8% in

patients with multiple myeloma and 1.2~12% in those with metastatic breast cancer.<sup>6-8</sup> However, the incidence of BONJ in patients with osteoporosis is much lower. The annual incidence of BONJ in patients with oral bisphosphonate is 0.7/100,000 patients- treatment years according to data from the AAOMS, and 1.6~3.84/100,000 patients-treatment years, based on data from Merck.<sup>5</sup> Although BONJ is a rare condition, cases of BONJ are being reported with increasing frequency. In this study, estimated prevalence of BONJ was 38/100,000 patients, which was similar with recent report of prevalence as 50~70/100,000 patients.<sup>9</sup>

The patients' age, gender, co-morbidity and initiating events in this report were consistent with those reported previously.<sup>10-14</sup> Most of the patients with BONJ in this study received alendronate. In addition, most patients had involvement of the mandible, which is consistent with prior reported case series. The mean age was significantly older in patients with BONJ compared to patients with IONJ. This is thought to be the characteristics of BONJ and IONJ patients; most of BONJ patients are postmenopausal women, and one young patient was included in the IONJ group. In our study, most BONJ and IONJ patients were female. In case of BONJ, large portion of female might be explained with early osteoporosis caused by menopause compared to males.

The mean duration of the treatment from the first administration of bisphosphonate medications to the clinical observation of BONJ was 3.7 years in our study. Some cases were detected as early as 1 year from the start of bisphosphonate use. This finding does not agree with several recent studies that reported the time interval to be at least 2~3 years from the start of bisphosphonate therapy for osteoporosis, which has been proposed as the minimum time interval for the clinical presentation of BONJ.<sup>10,15</sup>

The results of all previous studies points to the potential role of bisphosphonate medications as the main pathogenic factor associated with the development of ONJ. However, such necrosis of the jaw bone can result from a variety of factors other than bisphosphonate treatment. The results of this study also present the clinical features, initiating events and treatment modalities of patients with IONJ; none of these patients had a history of bisphosphonate treatment. Several clinical characteristics of the patients with IONJ were similar to those with the patients of BONJ, including treatment modalities and recovery rate. However, the mean age was significantly younger in patients with IONJ compared to the patients with BONJ. This is thought to be the characteristics of BONJ patients; most of them are postmenopausal women. In the BONJ group, the mandible was affected more than the maxilla, while the reverse was found in the IONJ group. A smaller number of patients were diagnosed with diabetes mellitus and the mean treatment duration was shorter in the IONJ group compared to the BONJ group. These results might be affected by study subjects' age, the existence of steroid user and large portion of DM patients in the BONJ group. Female predominance was also observed in the IONJ group and it was a different result from previous study.<sup>16</sup> It is thought to be the result of small number of cases in our study.

The pathogenesis of osteonecrosis, in general, is thought to be secondary to impaired blood flow and

metabolic effects. Osteoradionecrosis, as the name suggests, is a condition associated with previous radiotherapy to the head-and-neck region. Osteoradionecrosis was first described in 1983 in association with hypovascularity, hypocellularity and local tissue hypoxia.<sup>17,18</sup> The pathogenesis of other causes of osteonecrosis is not clear. ONJ can also result from trauma caused by a severe blast injury, surgical trauma or trauma that has resulted in severe displacement of portions of the mandible, particularly the mandibular condyle.<sup>13</sup> Systemic medications other than bisphosphonate may be associated with the development of ONJ. Recent studies have reported the development of ONJ in patients with metastatic cancers who received the anti-angiogenic drugs bevacizumab and sunitinib.<sup>19,20</sup> Avascular necrosis is most commonly observed in the head of the femur, and is often related to chronic glucocorticoid use. In addition, it has been theorized that specific bacterial or viral infections might be associated with ONJ. Furthermore, alcohol abuse, exposure to certain chemotherapeutic agents and exposure to smoke also have been correlated with ONJ.<sup>4</sup> In aspect of BONJ, the pathologic mechanism is uncertain. One proposed pathogenesis process suggests that the potent bisphosphonate mediated inhibition of osteoclastic function leads to decreased bone resorption and inhibits normal bone turnover remodeling, resulting in areas of microdamage accumulation and a reduction in some mechanical properties of bone.<sup>21</sup> Another mechanism that bisphosphonates inhibit angiogenesis *in vitro*<sup>22</sup> was reported. Other than that, there is a report that bisphosphonate may cause direct toxicity to soft tissue.<sup>23</sup>

A definitive treatment for BONJ has not yet been established. Conservative care with long-term antibiotics use is the main therapy for patients with BONJ.<sup>24-26</sup> Generally, surgical treatment is not recommended because of worsening symptoms and treatment outcomes. But in non-oncologic patients, surgical procedures may achieve better results.<sup>11</sup> Most of the patients were referred to our hospital from primary care

clinics because there was no improvement despite of conservative treatment. In this study, surgery was done in 9 out of 12 (75%) patients with BONJ. According to the recent reports, 75% and 79% each of patients with non-oncologic BONJ had surgical treatment.<sup>9,11</sup>

In this study, 11 out of 12 (92%) BONJ patients achieved a complete resolution, which was more favorable than previous report.<sup>14</sup> However, recent study reported that 21 out of 24 (88%) patients showed complete healing after follow-up of BONJ in non-oncologic patients.<sup>11</sup> In this study, all six patients with IONJ completely healed during the follow-up period.

There are some limitations in this study. First, the number of cases is relatively small, and data were collected from one university hospital. Further study with large number of subjects from multicenter is needed. Second, this is an observational study of retrospective medical record review. These may limit the ability to generalize the study results.

In conclusion, ONJ was a rare disease before introduction of bisphosphonate medication. However, ONJ may occur in the absence of bisphosphonate. BONJ occurred in older patients, and needed longer treatment duration compared to IONJ. The recovery rate from ONJ was relatively good in our study.

**Conflict of interest: All authors have no conflicts of interest.**

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