The Risk of Osteonecrosis of the Jaws in Taiwanese Osteoporotic Patients Treated With Oral Alendronate or Raloxifene

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Background: This study aimed to explore the possible association between osteonecrosis of the jaws (ONJ) and oral alendronate or raloxifene used for osteoporosis and to estimate its absolute and attributable risks in the Taiwanese population.

Methods: Using an electronic medical records system and manual confirmation of ONJ, we identified patients who began taking alendronate or raloxifene for osteoporosis and developed ONJ between January 2000 and April 2012.

Results: The incidence of ONJ associated with oral alendronate for the management of osteoporosis began after 1 year of drug exposure and progressively increased with longer durations of therapy, specifically from 0.23% to 0.92% as the duration of treatment went from 2 years to 10 years. The overall frequency of ONJ related to oral alendronate over a 12-year period was 0.55%. The incidence rate of ONJ attributed to alendronate exposure was 283 per 100 000 persons per year. On multivariate Cox proportional analysis, adjusting for the potential confounders, alendronate remains an independent predictor for ONJ occurrence [hazard ratio 7.42 (1.02–54.09)] compared with raloxifene. Advanced age, drug duration, and coexisting diabetes and rheumatoid arthritis are contributing factors to the development of oral alendronate-related ONJ.

Conclusion: We provided the evidence to support the association of ONJ with oral alendronate used in the treatment or prevention of osteoporosis. (***J Clin Endocrinol Metab*** **99: 2729–2735, 2014)**

Although bisphosphonates (BPs) can effectively increase bone mineral density and reduce fracture risk in patients with osteoporosis, there have been concerns about osteonecrosis of the jaws (ONJ) (1–3) and atypical femoral fractures (3, 4) with the long-term use of BPs. It has also been reported that high-dose iv BP use in oncology patient populations is a contributing factor to the development of ONJ (1, 2). However, there is insufficient evidence to confirm a causal link between the ONJ and relatively lower doses of BP used for osteoporosis because these problems can certainly also occur in the absence of BP use. In 2007, the American Society for Bone and Mineral Research Task Force on ONJ conducted a literature review of published and unpublished data and concluded that the risk with oral BPs for osteoporosis was very low (somewhere between 1 in 10 000 to $<$ 1 in 100 000 patient-treatment years) (1). But the task force recognized that the true incidence may be higher. In addition, a retrospective study (5) showing that most reported ONJ patients on oral alendronate as a treatment for osteoporosis

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Abbreviations: BP, bisphosphonate; CI, confidence interval; ICD-9, *International Classification of Diseases*, ninth revision; ONJ, osteonecrosis of the jaws; OR, odds ratio; RA, rheumatoid arthritis.

were Asian Americans, which raises concern about the higher prevalence of ONJ in Asians compared with Western populations receiving oral BPs. We hypothesized that there may be an increased risk of ONJ among osteoporotic Asian patients taking BPs. Therefore, the aims of our study were as follows: 1) to investigate whether the lower dose of BPs used in the management of osteoporosis leads to any increase in the risk of ONJ beyond what is observed in the group taking only raloxifene orally and never taking BPs at all (ONJ has not yet been reported with raloxifene); and 2) to identify potential contributing factors that may be unique to the Taiwanese population.

Materials and Methods

Cohort identification and ONJ verification

Considering the mean age of menopause in women and the usual onset of senile osteoporosis in men, we arbitrarily identified women aged 50 years or older or men aged 60 years or older who began taking alendronate between January 2000 and April 2012 in a retrospective pharmacy database at our hospital. To compare the incidences of ONJ between the alendronate and raloxifene groups, we analyzed only female patients aged 50 years or older because raloxifene was not licensed to treat male osteoporosis. Antiresorptive-related ONJ was defined as the presence of exposed bone in the maxillofacial region for more than 8 weeks in persons treated with alendronate or raloxifene without radiotherapy to the jaws (1, 2). Subjects who were diagnosed as having head and neck cancers [*International Classification of Diseases*, ninth revision (ICD-9), codes 140–149, 160, and 161] before and during the treatment period of antiresorptive therapy were excluded from the analysis because of probable radiotherapy or local damage to the jaws. We identified ONJ cases among these subjects by two-step verification. The first step was to search for patients with inflammatory dental conditions by a principal hospital diagnosis code of 526.3X, 526.4X, 730.1X, or 733.4X and also by claims for at least one dentistry visit at our hospital. The second step required manual review of radiographic, chart, and operative records and pathology reports for confirmation of ONJ and its major predisposing factors in eligible patients. All ONJ cases included in this study had radiographic evidence of ill-defined lytic lesions of the jawbone in addition to pathological evidence of the sequestra or osteomyelitis. This study was approved by the Institutional Review Board at National Taiwan University Hospital (protocol number 201311010RINB), Taipei, Taiwan.

Statistical analysis

Subjects who were ever exposed to drug therapy, including current and past users, were considered drug users. The duration of drug exposure was defined as time in years from the date of first prescribed dose either to the last recorded dose in ONJ-free individuals and in patients suffering from ONJ in the period of drug holiday or to the date of ONJ diagnosis in affected cases who ceased medication after event occurrence. We divided the number of ascertained ONJ cases by the sum of person-years in the drug groups to estimate crude incidences. ONJ incidence trends over time were analyzed using a linear-by-linear association test. A 95% confidence interval (CI) for each incidence rate of ONJ was computed using the Clopper-Pearson method. All continuous variables are reported as mean ± SD (with 95% CI where appropriate), and all categorical variables are reported as frequencies or percentages. Fisher exact tests for categorical variables and *t* tests for continuous variables were used to compare baseline characteristics in patients taking alendronate with and without definite ONJ. The independent determinants of given variables were analyzed using multiple logistic regression analysis. The adjusted variables are stated in each analysis. The Kaplan-Meier method was used to estimate the median interval to ONJ occurrence between alendronate and raloxifene groups. Stepwise Cox proportional hazards regression was used to investigate multivariate associations with time to development of ONJ. A value of $P < .05$ was considered statistically significant. SPSS version 16 (SPSS Inc) was used for the analyses.

Results

Risk factors associated with ONJ development

We initially identified 7389 patients who began receiving oral alendronate therapy after age 50 years in women and 60 years in men. After eliminating 49 persons with head and neck cancers, 7340 subjects fitted the requirements. Forty-eight of 7340 cases were verified to have ONJ proven by radiographic images and operative findings. Before development of ONJ among these 48 patients, eight cases had previously received other antiresorptive agents (three zoledronic acid, one both raloxifene and zoledronic acid, one pamidronate, one denosumab, one ibandronate and raloxifene, one raloxifene). These eight patients were excluded, with the remaining 7332 patients (6485 women, 847 men) being enrolled for analysis. The baseline characteristics of the 7332 eligible patients are listed in Table 1. In the end, a total of 40 alendronate-related ONJ cases (one man and 39 women) were identified. Among these, 22 cases had invasive dental procedures before they developed ONJ. At the time of alendronate initiation, the affected cases were 59.6–86.6 years of age, with an average age of 74.9 years, and the mean duration of alendronate therapy was 4.0 years. The frequencies of ONJ related to oral alendronate over a 12-year period were 0.60% in women, 0.12% in men, and overall 0.55%. The incidence of ONJ progressed with duration of alendronate use (Figure 1). The univariate analysis shows that there were significant differences in age at the time of alendronate initiation ($P = .010$), duration of therapy ($P < .001$), concomitant diabetes ($P = .014$), hypertension ($P = .004$), rheumatoid arthritis (RA) ($P = .007$), and diffuse diseases of connective tissue ($P = .042$) between patients with and without ONJ (Table 1).

To predict the occurrence of ONJ, we further analyzed these factors using a multiple logistic regression and found that advanced age at the time of drug initiation [odds ratio

Table 1. Comparisons of the Clinical Characteristics in Patients Taking Alendronate Without and With ONJ

Parameters[a]	Without ONJ (n = 7292)	With ONJ (n = 40)	*P* Value[b]
Female	6446 (88.4%)	39 (97.5%)	.081
Age at drug initiation, mean (SD), y	71.771 (10.041)	74.945 (7.362)	.010
Duration, mean (SD), y	1.805 (2.200)	3.974 (2.054)	.000
Diabetes mellitus	1365 (18.7%)	14 (35.0%)	.014
Dyslipidemia	1665 (22.8%)	13 (32.5%)	.184
Hypertension	3234 (44.3%)	27 (67.5%)	.004
RA	221 (3.0%)	5 (12.5%)	.007
Ankylosing spondylitis	69 (0.9%)	0	1.000
Diffuse diseases of connective tissue	238 (3.3%)	4 (10.0%)	.042
Chronic use of glucocorticoids[c]	506 (6.9%)	4 (10.0%)	.358
Hypothyroidism	178 (2.4%)	0	.627
Hyperthyroidism	190 (2.6%)	3 (7.5%)	.087
Anemia	710 (9.7%)	7 (17.5%)	.106
Chronic kidney diseases	116 (1.6%)	1 (2.5%)	.475
Esophagitis or ulcer	488 (6.7%)	2 (5.0%)	1.000
Peptic ulcer	1098 (15.1%)	4 (10.0%)	.506
Overall malignancy	1105 (15.2%)	2 (5.0%)	.077

ICD-9 codes included the following: diabetes mellitus, 250.xx; dyslipidemia, 272.x; hypertension, 401.x; rheumatoid arthritis, 714.xx; ankylosing spondylitis, 720.xx; diffuse diseases of connective tissue, 710.x; hypothyroidism, 243.x, 244.x; hyperthyroidism, 242.x; anemia, 280.x-285.x; chronic kidney disease, 585.x; esophagitis or ulcer, 530.1x, 530.2x; peptic ulcer, 531.xx-533.xx; overall malignancy, 150.x-159.x and 162.x-208.x.

[a] At the time of the diagnosis of ONJ in affected cases or the last recorded dose in ONJ-free individuals.

[b] *P* value was calculated from a Fisher exact test or a *t* test for categorical or continuous variables, respectively.

[c] Equivalent to 5 mg or more of prednisone daily for 3 months or longer.

(OR) 4.14; 95% CI 1.236–13.891 in age 65–80 y; OR 5.65; 95% CI 1.565–20.379 in age > 80 y] compared with an age younger than 65 years, longer duration (≥3 y) of alendronate therapy (OR 5.73; 95% CI 2.967–11.044), and preexisting medical conditions of diabetes (OR 2.00; 95% CI 1.036–3.871), and RA (OR 4.56; 95% CI 1.726–12.070) increased the risk of ONJ (Table 2).

Alendronate leads to a higher incidence of ONJ compared with raloxifene

Among 1884 osteoporotic women using raloxifene, ONJ was ascertained in 16 patients. Among these 16 patients, three had previously taken alendronate and raloxifene at our hospital before the development of ONJ, and 12 received raloxifene at our hospital for an alternative therapy of osteoporosis after the occurrence of alendronate-associated ONJ (five took alendronate at other institutions and seven at our hospital). These 15 individuals were dropped from the raloxifene group, and the seven individuals receiving a switch from alendronate to raloxifene at our hospital after ONJ occurrence were classified into the alendronate group. Finally, one of 1869 eligible patients using raloxifene was diagnosed as having ONJ without any alendronate exposure, whereas 6485 female patients with 39 ONJ events were recognized in the alendronate group. The baseline characteristics before the use of alendronate or raloxifene are listed in Table 3. There was no significant difference between the two groups except for mean age at the time of drug initiation (71.1 vs 70.3 y, $P = .009$), chronic use of glucocorticoids (5.8% vs 4.0%, $P = .002$), preexisting hyperthyroidism (2.3% vs 1.6%, $P = .038$), chronic kidney disease (0.9% vs 3.1%, $P < .001$), and chronic inflammation of the esophagus (4.4% vs 5.9%, $P = .010$). The crude incidence of ONJ in women taking alendronate was approximately 318 in 100 000 for each year of exposure to the medication, whereas it was only 35 per 100 000 persons per year in the raloxifene group, indicating an attributable risk of ONJ associated with alendronate to 283 per 100 000 person-years.

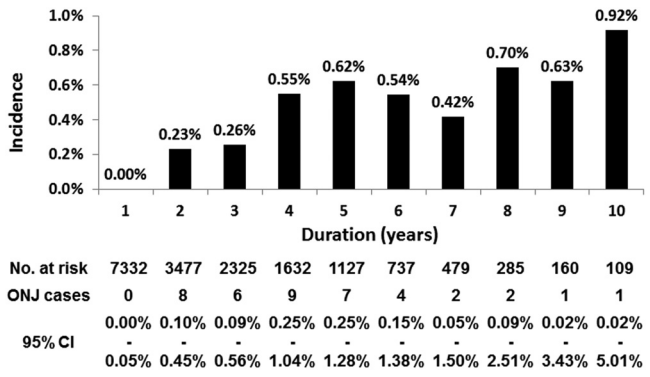

Figure 1. Incidence of ONJ associated with oral alendronate by duration of drug therapy. There was no ONJ case in the first treatment year. The incidence of ONJ associated with alendronate was 0.23% in the second treatment year. It increased with increasing exposure duration and was 0.92% in the 10th treatment year. The linear-by-linear association analyses indicated the incidence of ONJ associated with alendronate by duration of drug therapy appeared in an upward trend ($P < .001$). A 95% CI was calculated for each incidence rate of ONJ.

Time to the onset of ONJ in women receiving alendronate or raloxifene was explored using a Kaplan-Meier sur-

Table 2. Risk Factors for Developing ONJ in Patients Receiving Alendronate Therapy

Parameter	Adjusted OR	95% CI	*P* Value[a]
Gender, female vs. male	4.767	0.648–35.074	.125
Age, 65–80 vs < 65 y[b]	4.144	1.236–13.891	.021
≥ 80 vs < 65 y	5.647	1.565–20.379	.008
Duration, ≥ 3 y vs < 3 y	5.725	2.967–11.044	<.001
Diabetes mellitus	2.003	1.036–3.871	.039
RA	4.564	1.726–12.070	.002

[a] *P* value was calculated from a multiple logistic regression analysis.

[b] At the time of alendronate initiation, compared with age less than 65 years.

vival analysis. The interval to ONJ occurrence was significantly different between these two groups (log-rank test, $P = .011$; Figure 2). The risk of ONJ began after 1 year of alendronate initiation and the cumulative incidence of ONJ progressively increased with longer durations of alendronate treatment, ranging from 0.25% for 2 years of alendronate use to 6.0% for 10 years of alendronate use. To further investigate associations between the variables and time to develop antiresorptive-related ONJ, stepwise Cox proportional hazards regression was performed (as shown in Table 4). Compared with the individuals aged 50–65 years, the adjusted hazard ratios for ONJ were 6.34 for 65- to 80-year-old subjects and 10.34 for patients aged older than 80 years. Compared with the controls taking oral raloxifene only, the patients taking alendronate had a hazard ratio 7.42 times higher for the development of ONJ, after adjusting for other possible contributions from other variables. The individuals with diabetes and RA, respectively, had 2.04 and 7.56 times the risk of ONJ compared with those without these medical conditions, at any given point in time.

Discussion

Earlier studies indicated that high-dose iv bisphosphonate used for a cancer indication is a contributing factor to the development of ONJ with a frequency of 1%–10%, depending on the duration of therapy (1). However, studies concerning the risk of ONJ after oral bisphosphonate use are sparse. Lo et al (6) reported a prevalence of 0.10%, with an incidence of 28 per 100 000 person-years of oral bisphosphonate exposure in adults aged older than 21 years. In the subset of women aged 50 years and older who were treated with oral BPs, an ONJ frequency of 1 of 250 (0.40%) after recent tooth extraction was reported (7). Investigators in a study from Australia (8) established a frequency of 0.01%–0.04% in osteoporotic patients

Table 3. Baseline Characteristics Before the Use of Alendronate or Raloxifene

Parameters[a]	Alendronate (n = 6485)	Raloxifene (n = 1869)	*P* Value[b]
Age at drug initiation, mean (SD), y	71.062 (9.983)	70.340 (10.746)	.009
Diabetes mellitus	1017 (15.7%)	292 (15.6%)	.971
Dyslipidemia	1196 (18.4%)	336 (18.0%)	.659
Hypertension	2325 (35.9%)	643 (34.4%)	.261
RA	171 (2.6%)	41 (2.2%)	.317
Ankylosing spondylitis	43 (0.7%)	11 (0.6%)	.870
Diffuse diseases of connective tissue	191 (2.9%)	53 (2.8%)	.876
Chronic use of glucocorticoids[c]	373 (5.8%)	74 (4.0%)	.002
Hypothyroidism	123 (1.9%)	26 (1.4%)	.165
Hyperthyroidism	152 (2.3%)	29 (1.6%)	.038
Anemia	440 (6.8%)	133 (7.1%)	.604
Chronic kidney disease	60 (0.9%)	58 (3.1%)	.000
Esophagitis or ulcer	288 (4.4%)	111 (5.9%)	.010
Peptic ulcer	719 (11.1%)	228 (12.2%)	.185
Overall malignancy	842 (13.0%)	217 (11.6%)	.124

ICD-9 codes included the following: diabetes mellitus, 250.xx; dyslipidemia, 272.x; hypertension, 401.x; RA, 714.xx; ankylosing spondylitis, 720.xx; diffuse diseases of connective tissue, 710.x; hypothyroidism, 243.x and 244.x; hyperthyroidism, 242.x; anemia, 280.x-285.x; chronic kidney disease, 585.x; esophagitis or ulcer, 530.1x and 530.2x; peptic ulcer, 531.xx-533.xx; overall malignancy, 150.x-159.x and 162.x-208.x

[a] Factors at the time of drug initiation.

[b] *P* value was calculated from a Fisher exact test or a *t* test for categorical or continuous variables, respectively.

[c] Equivalent to 5 mg or more of prednisone daily for 3 months or longer.

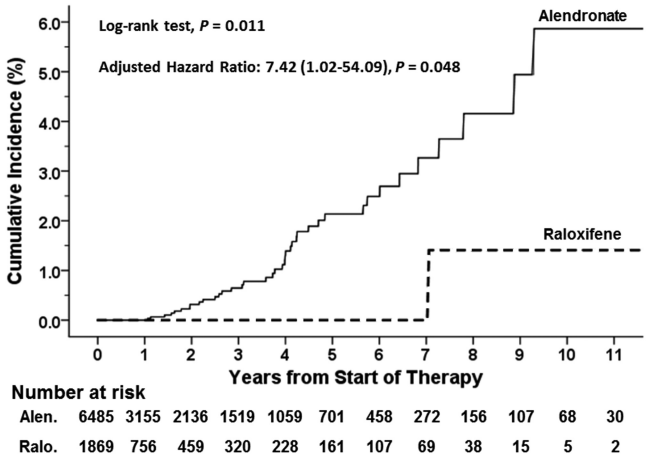

Figure 2. Time to the onset of ONJ in patients receiving alendronate or raloxifene. After adjusting for other possible contributions from other variables, individuals taking alendronate had a higher hazard ratio (7.423; 95% CI 1.019–54.091; $P = .048$) of occurrence of ONJ than controls on oral raloxifene. Alen, alendronate; Ralo, raloxifene.

mainly on oral alendronate or 0.09%–0.34% after tooth extraction. In a study from Germany (9), investigators conducted a postal survey and reported an incidence of 0.0038% for ONJ among patients receiving bisphosphonates for osteoporosis. Collectively, these data suggest that the overall frequency of ONJ associated with oral BPs might be as high as 0.1%, regardless of the medical reasons for oral BP use, age, gender, or dentoalveolar surgery, and it further rises to 0.34%–0.4% after recent dental procedures in Western populations.

In a patient population at the University of Southern California (5), 9 in 208 patients with a history of alendronate use (4%) had active ONJ. All of these nine ONJ cases occurred after denture trauma. In addition, seven of nine cases with alendronate-related ONJ were Asian American and raised concern about the prevalence of ONJ in the Asian population. However, the overall frequencies of ONJ after oral BP use reported in Asian populations were inconsistent, with 0.46%–0.99% in Japanese (10) and 0.05%–0.07% in Koreans (11). In this article, we estimated a frequency of ONJ of 0.55% in Taiwanese patients taking oral alendronate for the prevention or treatment of osteoporosis. This is close to the overall frequency estimated in the Japanese population and higher than that reported in Western and Korean populations, reflecting the potential influence of genetic background and differences in oral health on the development of ONJ.

It is not known whether the incidence of ONJ differs from that seen in the general population. Yamazaki et al (10) reported an attributable risk of ONJ between oral BP and non-BP users for an indication of osteoporosis ranging from 0.38% to 0.81%, thus showing an increased risk for ONJ among users of oral BPs. Conversely, in a retrospective cohort study (12), the incidence was 0.15 per 1000 person-years among patients exposed to oral BPs for osteoporosis and 0.26 among those unexposed individuals. In our cohort, the attributable risk of ONJ associated with alendronate was estimated to be 283 per 100 000 person-years, thereby supporting the hypothesis that oral BPs used for osteoporosis can be a contributing factor to the development of ONJ.

It is unclear whether the risk factors of ONJ among cancer patients receiving iv high-dose BPs are also triggers of that among osteoporotic subjects taking relatively low-dose BP in oral form. In our analysis using multiple logistic regression (Table 2), we could not make a conclusion regarding the gender effect on ONJ occurrence (OR 4.77; 95% CI 0.648–35.074; $P = .125$), although most cases with ONJ were women. The odds of ONJ increased markedly with increasing age among patients taking oral alendronate for osteoporosis. Other risk factors of ONJ associated with oral alendronate include prolonged duration ($\geq$3 y) of bisphosphonate therapy (OR 5.73), diabetes mellitus (OR 2.00), and RA (OR 4.56). In Taiwan, regulations governing the insurance reimbursement of alendronate or raloxifene in terms of skeletal status and age are identical. Although the mean ages of initiation of drugs between alendronate and raloxifene groups were significantly different (71.1 vs 70.3, $P = .009$, Table 3), the difference was small and less than 1 year, which apparently was not a major factor for the differences between the incidences of ONJ in these two groups. In terms of time to the onset of ONJ (Table 4), the covariates of diabetes and RA were found to have significant effects with hazard ratios of 2.04 and 7.56, respectively. Either of the older age subsets gives a significant increase of the hazard rate by a

Table 4. Association Between Hazard Rate and Risk Factors Based on the Multivariate Cox Model

Risk Factors[a]	Adjusted Hazard Ratio	95% CI	*P* Value
Alendronate vs raloxifene	7.423	1.019–54.091	.048
Age, 65–80 vs 50–65 y	6.337	1.488–26.992	.013
Age, ≥ 80 vs 50–65 y	10.342	2.278–46.949	.002
Diabetes mellitus	2.038	1.017–4.085	.045
RA	7.555	2.904–19.655	<.001

[a] At the time of initiation of alendronate or raloxifene.

factor of 6.34–10.34 compared with the group aged 50–65 years, indicating a consistent association of ONJ with advanced age. Notably, chronic steroid use did not have a major effect on the occurrence of ONJ by using stepwise multivariate Cox proportional hazard regression. We think this is due to the fact that most of the steroid users are RA patients and the effect was explained by the covariate of RA.

The retrospective nature of this study might have had an inherent bias and certain limitations. First, the potential for various source of surveillance bias cannot be completely prevented. One of the sources of such bias is the differences in the health-seeking behavior after ONJ occurrence because all patients suffering from ONJ may not visit our dental department. Another source is the inconsistencies in case detection and diagnoses among health care professionals. The BP users are more likely to have dental visits because of growing ONJ cases reported, resulting in higher probability of subclinical disease being detected. In this study, we included only late-stage ONJ with radiographic and pathological evidences to reduce this bias.

Second, although the results are consistent with those of the previously published studies, the overall frequency of 0.55% noticed in this study is likely an underestimated value because all patients suffering from ONJ who received alendronate from our hospital may not have been referred to the dental department at our hospital. In addition, ONJ-affected cases once using other antiresorptive agents (8 of 48) were excluded, even though they mainly took alendronate for osteoporosis; nevertheless, we did not eliminate users receiving iv BP or denosumab from the denominator—the total number of patients treated with these two antiresorptives.

Third, the dose and adherence of the drugs, as well as subsequent dose-response relationships, were not analyzed in this study. Fourth, there was no specific disease code available for drug-related ONJ at the time of the analysis. To overcome a potential misclassification bias, we reviewed medical and radiographic images to ascertain ONJ events and its predisposing drugs.

Fifth, there's still a degree of uncertainty about the rates of ONJ in the sixth to 10th treatment years of alendronate because there were only one to four ONJ cases per year in these periods. Likewise, the incidence of ONJ among osteoporotic women taking raloxifene is based on one case and so is not a robust estimate. Increasing case number is needed for a more precise estimate in further research.

Finally, we do not know the duration of the concomitant medical conditions (especially diabetes and RA), the presence of complications, or the treatments used. However, medications impacting bone turnover, such as statins (13) or thiazolidinediones (14), and infections of the gingivae (15) are more common in diabetic patients. Similarly, inflammatory alternations and drugs to treat the RA, such as glucocorticoids and methotrexate, may play a relevant role in the development of ONJ among patients with RA (16). For this reason, we used disease status (present or absent) instead of treatment used as a statistic variable for analysis. Despite these limitations, this hospital-based cohort study provides a comprehensive estimation of the specific risks of ONJ in osteoporotic patients taking oral alendronate compared with non-BP therapy, which will increase the awareness about ONJ and serve as a source of information for the physicians treating osteoporotic patients in Taiwan and Asia.

In conclusion, the present study supports the association of ONJ with oral BP in osteoporotic patients. The incidence of ONJ increases after 1 year of alendronate use and progresses with the duration of therapy. The risk of oral alendronate-related ONJ in our Taiwanese population is higher than that reported in Western and Korean populations but is similar to that reported in Japanese. The role of Asian ethnicity in ONJ development needs to be further investigated.

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