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Osteonecrosis of the Jaw in Older Osteoporosis Patients Treated with Intravenous Bisphosphonates

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Abstract

BACKGROUND—Intravenous bisphosphonate therapy has been linked to osteonecrosis of the jaw among patients with cancer. Some patients with osteoporosis also receive intravenous bisphosphonates, although at lower total doses than those with cancer.

OBJECTIVE—To examine the risk for jaw osteonecrosis among a population-based cohort of older adults receiving intravenous bisphosphonates for the treatment of osteoporosis.

METHODS—Using a 5% national sample of Medicare beneficiaries, we identified 2296 patients treated with intravenous infusions of bisphosphonates for osteoporosis and other metabolic bone diseases between January 1, 2000, and December 31, 2007. We matched this cohort to 6865 bisphosphonate nonusers, at a 1:3 ratio, on age, race, sex, type of bone disease, and risk factors for osteonecrosis of the jaw. Patients were followed until December 31, 2007. The jaw toxicity outcomes included operations on the facial bones or jaw and diagnosis of inflammatory conditions of the jaw.

RESULTS—The absolute risk at 3 years for any jaw toxicity was 0.70 events per 100 patients using bisphosphonates and 0.30 events per 100 patients not using such drugs (2-sided log rank test, $p = 0.08$). In multivariable survival analyses (Cox proportional hazards regression) adjusting for potential confounders, intravenous bisphosphonate use was not significantly associated with diagnoses or procedures suggestive of osteonecrosis of the jaw ($p = 0.24$).

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CONCLUSIONS—Patients with osteoporosis who are treated with intravenous bisphosphonates do not appear to have a statistically significant increase in the incidence of osteonecrosis of the jaw over 3 years compared with those who do not receive such treatment. Future studies will further contribute to our understanding of the bisphosphonate risk profile, thereby allowing patients and physicians to more rigorously assess the risk-benefit ratio of this treatment across different clinical scenarios.

Keywords

bisphosphonates; older adults; osteonecrosis; osteoporosis

Oral bisphosphonates are widely used for the treatment of osteoporosis and metabolic bone disease.[1,2] More recently, intravenous bisphosphonate therapy has been shown to be effective in treating osteoporosis.[3] Intravenous bisphosphonates have been used in higher doses since the early 1990s to treat bone metastases and hypercalcemia in patients with cancer.[4–6] Since 2003, several studies have reported that bisphosphonate use is associated with osteonecrosis of the jaw,[2,7–17] a condition characterized by the accumulation of necrotic exposed bone in the oral cavity.[2] The vast majority of cases of bisphosphonate-associated osteonecrosis of the jaw were reported to have occurred among patients with cancer.[2,8,18] Although the mechanisms underlying the increased risk of this condition among bisphosphonate users are not fully understood, they may include suppression of bone turnover and impaired blood supply.[2,10,19,20] In response to these findings, the Food and Drug Administration now requires that all bisphosphonate labels include osteonecrosis of the jaw as a possible adverse event.[4]

The total dose of an intravenous bisphosphonate administered to patients with osteoporosis is approximately one tenth of that given to patients with cancer.[3,21–24] The extent to which this lower bisphosphonate dose in patients with osteoporosis is associated with osteonecrosis of the jaw is uncertain.[25–27] A clinical trial of over 7000 patients with osteoporosis followed for 3 years reported no association between low-dose intravenous bisphosphonate exposure and osteonecrosis of the jaw.[3] Two population-based studies, which focused predominantly on oral bisphosphonates, have reported a low incidence (ranging from 1 to 34 per 100,000) of this adverse event among individuals without cancer.[25–27] Neither of these studies, however, included a comparison group (ie, patients with osteoporosis who were not prescribed bisphosphonates) or investigated the effect of intravenous bisphosphonate therapy. We therefore conducted a population-based cohort study of older patients diagnosed with osteoporosis to examine the association of intravenous bisphosphonate treatment with a subsequent diagnosis of osteonecrosis of the jaw.

Methods

STUDY DESIGN

We conducted a retrospective cohort study using enrollment and claims data for a 5% national sample of Medicare beneficiaries. The Centers for Medicare & Medicaid Services selected these beneficiaries based on the eighth and ninth digits (05, 20, 45, 70, 95) of their health insurance claim number. Data files were constructed to include patient demographic

and enrollment information (denominator file), claims for hospital stays (Medicare Provider Analysis and Review file), outpatient visits (Outpatient Standard Analytic file), and physician services (Medicare carrier claim file). This study was reviewed and approved by the University of Texas Medical Branch Institutional Review Board.

POPULATION

Using the Health Care Procedure Coding System (HCPCS) drug administration codes J2430 (pamidronate), J3487 (zoledronic acid), J1436 (etidronate disodium), and J1740 (ibandronate sodium), we identified Medicare beneficiaries (by International Classification of Diseases, 9th revision [ICD -9] code) who were diagnosed with osteoporosis (733.0x), osteopenia (733.90, 733.93, 733.99), disorders of calcium metabolism (275.4), and Paget disease (731.0) or fractures (800.xx–829.xx), and who were treated with at least 1 injection of one of the aforementioned bisphosphonates between January 1, 2000, and December 31, 2007. In our study, bisphosphonate users received an average of 1.81 infusions per person year.

Patients who were not enrolled in Medicare Parts A and B for the 12 months before the first bisphosphonate injection, who were members of a health maintenance organization any time during the 12 months before the first injection, or who were diagnosed with cancer within 12 months before the first injection were excluded from this study. Individuals who experienced a study outcome in the 12 months before the study start date were also excluded.

We matched each bisphosphonate user to 3 nonusers, using the same exclusion criteria for nonusers as for users. The initial study entry for nonusers was assigned randomly to match the distribution for the month and year of the first bisphosphonate injection received by the user. We then used a 3-step sequential matching process. In the first step, patients who had not received bisphosphonates were matched with those who had by age at bisphosphonate administration (<65, 65–69, 70–74, 75–79, or ≥80 years), sex (male or female), race (African American, white, other), quarter of the first bisphosphonate injection, number of risk factors (0, 1, or ≥2) for osteonecrosis (diabetes, alcoholism, cigarette smoking, obesity, hyperlipidemia, or pancreatitis), and type of bone disease. With this step we were able to identify 6453 matched nonusers. In the second step, some of the remaining users and nonusers were matched using less stringent criteria: age at bisphosphonate administration (<65, 65–74, ≥75 years), sex (male or female), race (white or nonwhite), number of risk factors (0 or ≥1) for osteonecrosis (diabetes, alcoholism, cigarette smoking, obesity, hyperlipidemia, or pancreatitis), and type of bone disease. This group consisted of an additional 362 nonusers. Finally, we matched the remaining users and nonusers using the following criteria: age at bisphosphonate administration (<65, 65–74, ≥75 years), sex (male or female), and type of bone disease. This group contained 50 matched nonusers. Overall, the match percentage was 99.68%, with 2296 users and 6865 nonusers. All of the unmatched users had Paget disease.

RISK FACTOR SCORES

A risk factor index for osteonecrosis was developed by summarizing the occurrence among subjects of the following conditions reported to be associated with an increased risk for osteonecrosis: diabetes (ICD -9 code 250.x), alcoholism (codes 291.x and 303.x), cigarette smoking (code 305.1), obesity (code 278.0), hyperlipidemia (codes 272.0–272.4), and pancreatitis (codes 577.0 and 577.1).[28] In addition, a comorbidity score was calculated using the Elixhauser comorbidity index after removing the diagnoses listed above.[29,30] For both the risk factor index and comorbidity score, we searched the inpatient, outpatient, and physician files for any of those diagnoses in the 12 months before study entry, as previously described.[31] Use of corticosteroids, an established risk factor for osteonecrosis,[25] was defined as receipt of at least 1 infusion of a corticosteroid in the period between 12 months before and 1 month after date of study entry and was based on the following HCPCS codes: J1094, J1100, J1700, J1710, J1720, and J2650.

OUTCOMES

The study outcomes were diagnoses of inflammatory conditions or osteomyelitis of the jaw (ICD -9 526.4) and operations on the facial bones and joints (ICD -9 procedure codes 76.0–76.6 and 76.9, or Current Procedure Terminology codes 21025, 21026, 21030, 21032–21034, 21040, 21045–21047, 21081, 21127, 21193–21196, 21198, 21199, 21206, 21210, 21215, and 21244–21249).[31]

STATISTICAL ANALYSIS

Unadjusted event-free survival was estimated using the Kaplan-Meier method.[32] Multivariable survival analyses were performed by Cox proportional hazards regression, with the dependent variable being time to first occurrence of a study outcome (ie, inflammatory conditions or osteomyelitis of the jaw or surgery on the jaw or facial bones). Adjusted failure rates, defined as 1 – the survival rate, were estimated using the Cox model.[32,33] We tested the assumption of proportionality in the Cox model by determining that the logarithm of the baseline cumulative hazard rates and the Schoenfeld residuals were proportional with follow-up time.[32,33] Because of the limited number of events in this study, arcsine-square root transformation of the survival function was used to construct the 95% confidence intervals of the failure rates in both survival analyses.[32] Patients were censored at death, at loss of Medicare Part A or Part B coverage, at time of enrollment in a health maintenance organization, or at the end of the study (December 31, 2007). Patient characteristics and treatment with bisphosphonate therapy were treated as independent variables. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). All statistical tests were 2-sided.

Results

Baseline characteristics of bisphosphonate users and matched nonusers are presented in Table 1. The distribution of bone disease, year of drug administration, age at drug administration, race, sex, and risk factor index were not statistically significantly different between users and nonusers. Overall, the median duration of follow-up for the entire study cohort was 729 days. This value was greater for nonusers (729 days) than for users (720) (p

= 0.03). However, differences between users and nonusers were observed for the 2 factors on which patients were not matched (ie, comorbidity index and use of an intravenous steroid); these were adjusted for in the subsequent analyses.

We evaluated event-free survival among the matched intravenous bisphosphonate users and nonusers for the outcomes using Kaplan-Meier curves (Figure 1, Table 2). As noted above, we used a diagnosis of inflammatory conditions or osteomyelitis of the jaw or an operation on the jaw and facial bones as indicators for osteonecrosis of the jaw because, during the study period, there was no specific ICD-9 code for the diagnosis of osteonecrosis of the jaw. At 3 years, 0.70% (95% CI 0.36 to 1.37) of users had any 1 of the 3 aforementioned indicators of osteonecrosis of the jaw, compared with 0.30% (95% CI 0.17 to 0.52) of nonusers (2-sided log-rank test, p = 0.08).

Next, using the Cox regression model, we investigated the association between intravenous bisphosphonate therapy and osteonecrosis of the jaw, considering other factors associated with increased risk for this outcome (Table 3). After adjusting for potential confounders, we found no significant association between intravenous bisphosphonate use and either a history of surgery on facial bones or a diagnosis of inflammatory conditions or osteomyelitis of the jaw (p = 0.24). Additionally, the model showed that neither comorbidity nor steroid use was associated with the outcome. The difference in the estimated rates of jaw toxicity between users and nonusers was 0.263 per 100 patients (95% CI –0.463 to 0.990).

Discussion

In this retrospective study of 2296 Medicare beneficiaries who received intravenous bisphosphonates for osteoporosis or metabolic bone disease, we found no statistically significant association between intravenous bisphosphonate therapy and a subsequent diagnosis of jaw toxicity. This study is, to our knowledge, the first investigation of a large population-based cohort of intravenous bisphosphonate users and matched nonusers without cancer. The results are in accord with a large randomized prospective trial of a once-yearly intravenous bisphosphonate infusion in patients with osteoporosis that found no increase in jaw toxicity in the treated sample.[3]

There are no prior population-based observational studies of intravenous bisphosphonates in patients without cancer, although there are several involving oral bisphosphonates. A national survey of oral and maxillofacial surgeons and dental specialists in Australia estimated that the incidence of osteonecrosis of the jaw in patients with osteoporosis who were prescribed bisphosphonates was between 10 and 40 per 100,000.[26] In this investigation, the numerator was obtained from a postal survey of all reported osteonecrosis of the jaw cases occurring in 2004 and 2005, and the denominator was obtained by assessing, from a national prescription database, the total number of persons who were prescribed oral bisphosphonates during this 2-year period. A German study of patients with osteoporosis and other bone diseases estimated the incidence of osteonecrosis of the jaw as less than 1 in 100,000.[27] In this study, the denominator, derived from a national prescription database, consisted of all patients living in Germany who were prescribed oral bisphosphonates between January 1, 2004, and December 31, 2006. The numerator

consisted of patients identified from a national osteonecrosis of the jaw registry during the same time period. Finally, 2 postmarketing surveillance studies conducted by pharmaceutical companies reported an incidence of osteonecrosis of the jaw of less than 1 per 100,000.[25,27] None of the aforementioned studies included a control group. Taken together, these studies provide evidence that the likelihood of developing osteonecrosis of the jaw as a result of exposure to low-dose bisphosphonate treatment is low.

Our study has several limitations. First, information on outcomes and risk factors came from diagnosis codes included in charges for outpatient and hospitalization services. Such diagnoses are not always accurate or complete.[29] In particular, some patients may have had unreported disease that would have been recognized only by screening. Likewise, some patients may have been treated by dentists rather than by oral surgeons, in which case a Medicare charge would not have been generated. If such underreporting occurred, however, we would have underestimated the number of osteonecrosis cases among both bisphosphonate users and nonusers.[18] Second, because we had no data on oral bisphosphonate use, we were unable to assess the extent to which use of these formulations contributed to the outcomes. Third, given the retrospective design of this study, it is possible that undetected selection bias may have affected the findings. However, our inclusion of multiple disease risk factors for osteonecrosis of the jaw as well as our inclusion criteria would have reduced the likelihood of such selection bias. Fourth, given that there were no specific ICD -9 codes for facial or jaw osteonecrosis or aseptic necrosis of the jaw until 2008, we relied on indirect measures, including operations on the jaw or facial bones or a diagnosis of inflammatory conditions or osteomyelitis of the jaw.[18] Fifth, because of the low incidence of osteonecrosis of the jaw, this investigation had limited statistical power with which to examine the association of intravenous bisphosphonates and jaw toxicity. In particular, the small number of cases (n = 9) among bisphosphonate users precluded a dose-response analysis. In view of this, it is informative to consider the 95% confidence intervals for risk of jaw toxicity following bisphosphonate use. In this study of osteoporosis patients, the upper 95% confidence interval limit for rate of jaw toxicity in intravenous bisphosphonate users was 1.37 per 100 over 3 years. This is considerably lower than the rate of jaw toxicity associated with intravenous bisphosphonate therapy that we observed in cancer patients,[18] who were receiving approximately 10-fold higher doses.[2,18,21,34] Finally, several previous studies of patients with cancer have reported that osteonecrosis of the jaw is more likely to occur among patients treated with zoledronic acid than with other bisphosphonate formulations.[15–17] The small number of cases, however, precluded an analysis of the relative toxicity across the different formulations. Given the low incidence of osteonecrosis of the jaw in both exposed and unexposed populations, it will be important for future investigations to examine bisphosphonate-associated osteonecrosis of the jaw in larger study samples and for longer follow-up periods.

The clinical benefits of bisphosphonates for treating osteoporosis, bone metastases, and numerous other bone conditions have been observed across a broad range of doses and formulations.[26] Clinical trials have shown that treatment with oral and intravenous bisphosphonates is associated with substantial reductions in vertebral, hip, and other fractures and substantial increases in bone mineral density at multiple sites.[1,3] Given that the risks of such treatments may vary by medication and patient characteristics, investigators

have sought to characterize a risk profile for bisphosphonates across a range of diagnostic and treatment subgroups. Osteonecrosis of the jaw, for example, is reported to occur more frequently among patients receiving high-dose intravenous bisphosphonates for cancer than among those receiving comparatively lower doses for other conditions.[25] Consistent with such findings, our study showed that intravenous bisphosphonates for treatment of osteoporosis and other bone diseases had a lower incidence of jaw toxicity than was observed in our previous study of patients with cancer. The observed risk disparity between individuals with and those without cancer may be attributable to a number of factors, including a 5- to 10-fold difference in the average dose of bisphosphonates, differences in immunologic competence and wound healing ability, and differences in exposure to other medications such as cytotoxic drugs and corticosteroids.[34] Future research should examine the extent to which the aforementioned factors mediate the increased risk of osteonecrosis of the jaw among cancer patients and whether the observed risk estimates remain stable over a longer duration of follow-up (eg, 10 years). Such information will further contribute to our understanding of the risk profile for bisphosphonates, thereby allowing patients and physicians to more rigorously assess the risk-benefit ratio of this treatment across different clinical scenarios.

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References

1. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med. 2004; 350:1189–1199. [PubMed: 15028823]
2. Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med. 2006; 144:753–761. [PubMed: 16702591]
3. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007; 356:1809–1822. [PubMed: 17476007]
4. Food and Drug Administration. [accessed 2009 Dec 11] Early communication of an ongoing safety review on bisphosphonates: alendronate (Fosamax, Fosamax Plus D), etidronate (Didronel), ibandronate (Boniva), pamidronate (Aredia), risedronate (Actonel, Actonel w/Calcium), tiludronate (Skelid), and zoledronic acid (Reclast, Zometa). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070303.htm
5. Smith MR, McGovern FJ, Zietman AL, et al. Pamidronate to prevent bone loss during androgen deprivation therapy for prostate cancer. N Engl J Med. 2001; 345:948–955. [PubMed: 11575286]
6. Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinner N. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol. 2003; 169:2008–2012. [PubMed: 12771706]
7. Bagan JV, Murillo J, Jimenez Y, et al. Avascular jaw osteonecrosis in association with cancer chemotherapy: series of 10 cases. J Oral Pathol Med. 2005; 34:120–123. [PubMed: 15641993]
8. 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; 62:527–534. [PubMed: 15122554]

9. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg. 2003; 61:1115–1117. [PubMed: 12966493]
10. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteoporosis) of the jaws: risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg. 2005; 63:1567–1575. [PubMed: 16243172]
11. 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. [PubMed: 15929121]
12. Farrugia MC, Summerlin DJ, Krowiak E, et al. Osteonecrosis of the mandible or maxilla associated with the use of new generation bisphosphonates. Laryngoscope. 2006; 116:115–120. [PubMed: 16481822]
13. Otto S, Abu-Id MH, Felker B, Warke PH, Becker ST, Kolk A. Osteoporosis and bisphosphonates-related osteonecrosis of the jaw: not just a sporadic coincidence—a multi-centre study. J Craniomaxillofac Surg. 2011; 39:272–277. [PubMed: 20580566]
14. Pazianas M, Miller P, Blumentals WA, Bernal M, Kothawala P. A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates: prevalence, risk factors, and clinical characteristics. Clin Ther. 2007; 29:1548–1558. [PubMed: 17919538]
15. Durie BG, Katz M, Crowley J. Osteonecrosis of the jaw and bisphosphonates. N Engl J Med. 2005; 353:99–102. [PubMed: 16000365]
16. Bamias A, Kastritis E, Bamia C, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates. J Clin Oncol. 2005; 23:8580–8587. [PubMed: 16314620]
17. Zervas K, Verrou E, Teleioudis Z, et al. Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single experience in 303 patients. Br J Haematol. 2006; 134:620–623. [PubMed: 16889620]
18. Wilkinson GS, Kuo YF, Freeman JL, Goodwin JS. Intravenous bisphosphonate therapy and inflammatory conditions or surgery of the jaw: a population-based analysis. J Natl Cancer Inst. 2007; 99:1016–1024. [PubMed: 17596574]
19. Hellstein JW, Marek CL. Bisphosphonate osteochemonecrosis (bisphossy jaw): is this phossy jaw of the 21st century? J Oral Maxillofac Surg. 2005; 63:682–689. [PubMed: 15883944]
20. Cheng A, Mavrokokki A, Carter G, et al. The dental implications of bisphosphonates and bone disease. Aust Dent J. 2005; 50(suppl 2):S4–S13. [PubMed: 16416712]
21. Giordano SH, Fang S, Duan Z, Kuo YF, Hortobagyi GN, Goodwin JS. Use of intravenous bisphosphonates in older women with breast cancer. Oncologist. 2008; 13:494–502. [PubMed: 18515734]
22. Savarese, DMF.; Berenson, JR. Bisphosphonates in breast, prostate, and other solid tumors. In: Basow, DS., editor. UpToDate. Waltham, MA: UpTo-Date; 2011.
23. Body JJ, Bartl R, Burckhardt P, et al. Current use of bisphosphonates in oncology: International Bone and Cancer Study Group. J Clin Oncol. 1998; 16:3890–3899. [PubMed: 9850035]
24. Rosen, HN. Bisphosphonates in the management of osteoporosis in postmenopausal women. In: Basow, DS., editor. UpToDate. Waltham, MA: Up-ToDate; 2011.
25. Khan AA, Sandor GK, Dore E, et al. Bisphosphonate associated osteonecrosis of the jaw. J Rheumatol. 2009; 36:478–490. [PubMed: 19286860]
26. Mavrokokki T, Cheng A, Stein B, Goss A. Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. J Oral Maxillofac Surg. 2007; 65:415–423. [PubMed: 17307586]
27. Felsenberg D, Hoffmeister B, Amling M, Mundlos S, Fratzl P. Kiefernekrosen nach hoch dosierter Bisphosphonattherapie. Dtsch Arztebl. 2006; 103:A3078–A3080.
28. Jones, JP. Osteonecrosis. In: Koopman, WJ., editor. Arthritis and allied conditions: a textbook of rheumatology. 13th ed. Baltimore, MD: Williams & Wilkins; 1997. p. 1923-1942.
29. Klabunde CN, Warren JL, Legler JM. Assessing comorbidity using claims data: an overview. Med Care. 2002; 40(suppl 8):IV-26–IV-35.
30. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998; 36:8–27. [PubMed: 9431328]

31. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. J Clin Epidemiol. 2000; 53:1258–1267. [PubMed: 11146273]

32. Klein, JP.; Moeschberger, ML. Survival analysis: techniques for censored and truncated data. New York: Springer; 1997.

33. Allison, PD. Survival analysis using the SAS System: a practical guide. Cary, NC: SAS Press; 1995.

34. Grbic JT, Landesberg R, Lin SQ, et al. Incidence of osteonecrosis of the jaw in women with postmenopausal osteoporosis in the health outcomes and reduced incidence with zoledronic acid once yearly pivotal fracture trial. J Am Dent Assoc. 2008; 139:32–40. [PubMed: 18167382]

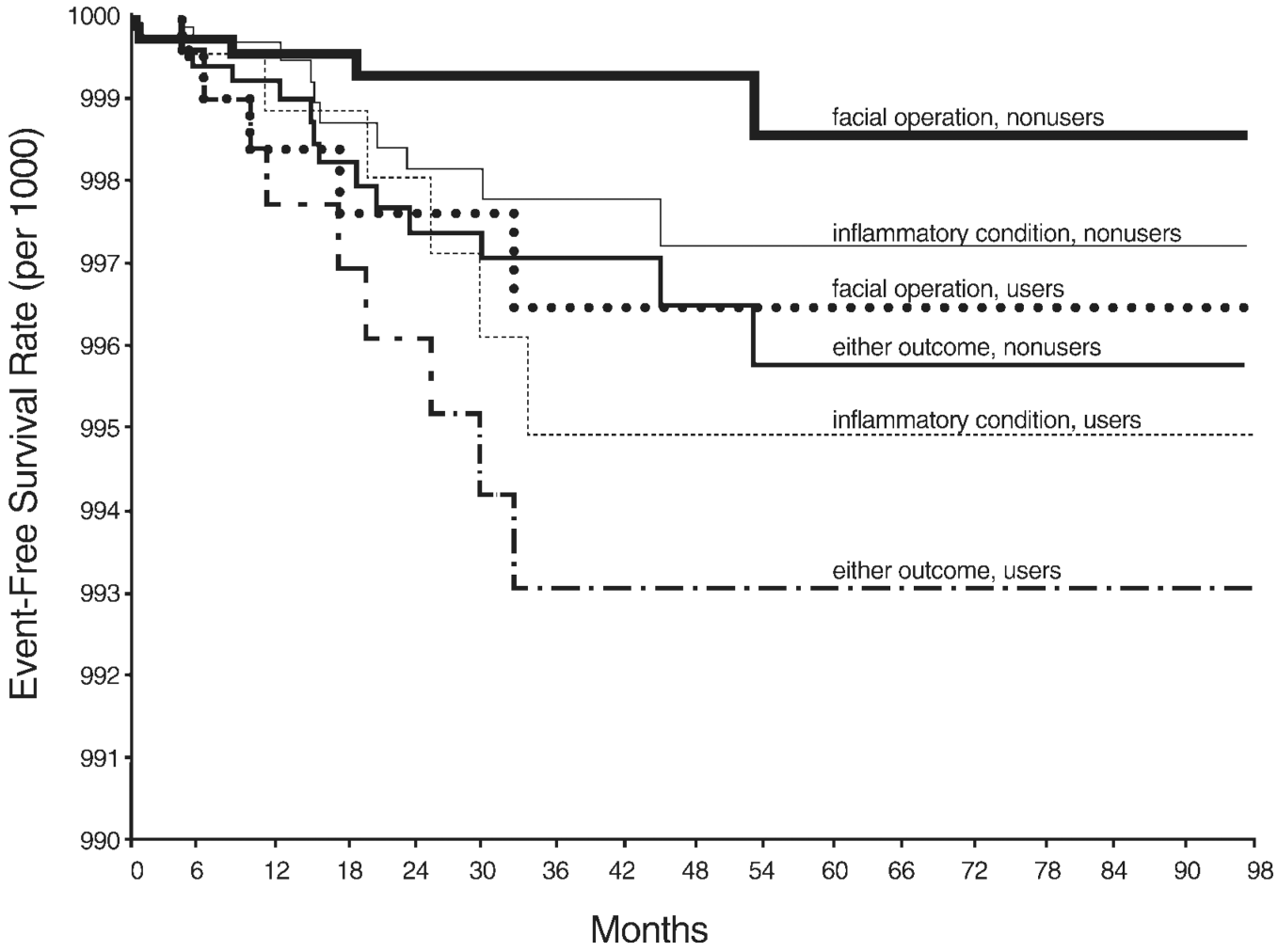

Figure 1.

Kaplan-Meier estimates for adverse bone outcomes for matched patients with osteoporosis or other bone disease who did or did not receive intravenous bisphosphonates. A significant difference between users and nonusers in experiencing either outcome was not observed at 3 years (p = 0.079, log-rank test) or at the end of the study (p = 0.144, log-rank test).

Table 1

Baseline Characteristics for All Intravenous Bisphosphonate Users and Matched Nonusers

Characteristic	Matched Users, n (%)	Matched Nonusers,[a] n (%)	p Value[b]
All	2296 (100)	6865 (100)	
Bone disease			
osteoporosis	1815 (79.05)	5445 (79.32)	0.98
osteopenia	113 (4.92)	339 (4.94)	
calcium metabolism disease	232 (10.10)	696 (10.14)	
Paget disease	94 (4.09)	259 (3.77)	
fractures	42 (1.83)	126 (1.84)	
Year of drug administration			
2000	114 (4.97)	342 (4.98)	>0.99
2001	144 (6.27)	428 (6.23)	
2002	194 (8.45)	578 (8.42)	
2003	278 (12.11)	830 (12.09)	
2004	299 (13.02)	897 (13.07)	
2005	307 (13.37)	913 (13.30)	
2006	195 (8.49)	582 (8.48)	
2007	765 (33.32)	2295 (33.43)	
Age at drug administration, y			
<65	257 (11.19)	771 (11.23)	0.96
65–69	294 (12.80)	883 (12.86)	
70–74	437 (19.03)	1295 (18.86)	
75–79	514 (22.39)	1491 (21.72)	
≥80	794 (34.58)	2425 (35.32)	
Race			
white	2141 (93.25)	6401 (93.24)	0.71
African American	82 (3.57)	263 (3.83)	
other/unknown	73 (3.18)	201 (2.93)	
Sex			
male	280 (12.20)	831 (12.10)	0.91
female	2016 (87.80)	6034 (87.90)	
Risk factor index[c]			
0	806 (35.10)	2421 (35.27)	0.87
1	1121 (48.82)	3372 (49.12)	
≥2	369 (16.07)	1072 (15.62)	
Comorbidity index[d]			
0	342 (14.90)	1735 (25.27)	<0.001

Characteristic	Matched Users, n (%)	Matched Nonusers,[a] n (%)	p Value[b]
1	573 (24.96)	2128 (31.00)	
2	528 (23.00)	1347 (19.62)	
≥3	853 (37.15)	1655 (24.11)	
User of intravenous steroid			
no	2196 (95.64)	6643 (96.77)	0.012
yes	100 (4.36)	222 (3.23)	

[a] We matched 94.00% of nonusers with users on type of bone disease, age, sex, ethnicity, number of risk factors, and time of drug administration. An additional 5.27% of the nonusers were matched with users on type of bone disease, sex, broad range of age (<65, 65–74, or ≥75 years), ethnicity (white or nonwhite), and number of risk factors (0 or ≥1), and 0.73% of the nonusers were matched with users on type of bone disease, sex, and broad range of age (<65, 65–74, or ≥75 years). The rest (0.33%, n = 23) of the nonusers were not matched with the remaining unmatched users, all of whom had Paget disease.

[b] p Values (χ^2 test) compare the distribution of characteristics between matched users and nonusers. All statistical tests are 2-sided.

[c] Summary index of risk factors for osteonecrosis, which include diabetes, alcoholism, cigarette smoking, obesity, hyperlipidemia, and pancreatitis.

[d] Diabetes was removed from the Elixhauser comorbidity index.

Table 2

Adverse Bone Outcomes

Bisphosphonate Use	At Risk, n	Failure Rate, % (95% CI)
No		
year 1	4224	0.081 (0.025 to 0.169)
year 2	3411	0.263 (0.132 to 0.437)
year 3	2433	0.296 (0.154 to 0.485)
Yes		
year 1	1398	0.231 (0.059 to 0.515)
year 2	1122	0.391 (0.138 to 0.772)
year 3	776	0.696 (0.306 to 1.244)

Table 3

Differences in Estimated Failure Rates Between Bisphosphonate Users and Nonusers[a]

Outcome	Bisphosphonate Use	Events, n	Failure Rates, % (95% CI)					
			At Year 3	Difference at Year 3	At End of Study	Difference at End of Study	Adjusted HR (95% CI)	p Value
Inflammatory conditions or osteomyelitis of jaw[b]	No	10	0.241 (0.062 to 0.534)		0.275 (0.071 to 0.609)		1.000 (referent)	
	Yes	6	0.433 (0.117 to 0.948)	0.192 (−0.286 to 0.670)	0.494 (0.133 to 1.081)	0.219 (−0.326 to 0.765)	1.666 (0.593 to 4.681)	0.33
Operations on facial bones[c]	No	5	0.091 (0 to 0.436)		0.127 (0 to 0.604)		1.000 (referent)	
	Yes	5	0.280 (0 to 1.267)	0.188 (−0.481 to 0.857)	0.387 (0 to 1.747)	0.260 (−0.663 to 1.184)	2.808 (0.798 to 9.880)	0.11
Either outcome[d]	No	15	0.324 (0.047 to 0.847)		0.406 (0.059 to 1.061)		1.000 (referent)	
	Yes	9	0.587 (0.137 to 1.349)	0.263 (−0.463 to 0.990)	0.736 (0.172 to 1.690)	0.330 (−0.580 to 1.240)	1.646 (0.712 to 3.803)	0.24

HR = hazard ratio.

[a] Matched bisphosphonate users (n = 2296) and nonusers (n = 6865).

[b] Cox proportional hazard model was adjusted for age, sex, ethnicity, risk index, and comorbidity.

[c] Cox proportional hazard model was adjusted for age, sex, risk index, comorbidity, and use of intravenous steroids.

[d] Cox proportional hazard model was adjusted for age, sex, ethnicity, risk index, comorbidity, and use of intravenous steroids.

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