Incidence of Hypocalcemia in Patients with Post-Menopausal Osteoporosis or Cancer Skeletal Related Events after Denosumab in Comparison to Zoledronic Acid in a Community Hospital Setting

Sunita Sharma and William Newman

1Department of Cardiovascular Medicine, Lahey Hospital and Medical Center, Burlington, MA 01805, USA
2Department of Internal Medicine, University of North Dakota School of Medicine and Health Sciences and Sanford Health, Fargo, North Dakota 58122, USA

Corresponding author: Sunita Sharma, Department of Cardiovascular Medicine, Lahey Hospital and Medical Center, Burlington, MA 01805, USA, Tel: 701-526-1526; E-mail: drsmsin@hotmail.com

Introduction
Denosumab, a monoclonal antibody, was recently approved by US Food and Drug Administration for treatment of postmenopausal osteoporosis and cancer related events (SRE). A variable incidence of hypocalcemia (5.5-13%) has been reported with denosumab as compared to the commonly used bisphosphonate, zoledronic acid (3.4-6%).

Methods
We reviewed the medical records of patients who received either denosumab or zoledronic acid in a community hospital setting to determine the incidence of hypocalcemia in patients with post-menopausal osteoporosis or cancer SRE.

Results
We found hypocalcemia with both denosumab and zoledronic acid post-injection but roughly twice as high in the denosumab group. Since, calcium levels were not obtained at the time of peak effect of treatment in every patient, we believe that actual incidence of hypocalcemia might have still been underestimated in this retrospective study with a limited number of patients.

Conclusion
We recommend that a prospective cohort study should be conducted in a larger community population with serum calcium level monitoring at regular intervals to determine the actual extent of hypocalcemia in patients receiving denosumab as compared to zoledronic acid.

Keywords: Hypocalcemia; Denosumab; Zoledronic acid; Osteoporosis; SRE

Introduction
Bisphosphonates have been the mainstay of the management of post-menopausal osteoporosis and cancer related events (SRE) since the mid-1990s. Of all the bisphosphonates, zoledronic acid is considered the most potent bisphosphonate and the most preferred due to ease of administration [1]. Recently, a monoclonal antibody, Denosumab, was approved by US Food and Drug Administration for treatment of postmenopausal osteoporosis and cancer SRE [2]. Denosumab specifically binds RANKL (Receptor activator of nuclear factor-kappaB ligand), blocks the binding of RANKL to RANK and thereby reduces the formation, function and survival of osteoclasts, which results in decreased bone resorption and increased bone density [3].

Denosumab has been reported to have a higher incidence of hypocalcemia (5.5-13%) in comparison to zoledronic acid (3.4-6%) [4-8]. We believe that due to controlled clinical settings these clinical trials might not reveal the true incidence of adverse effects of denosumab. With increasing use of denosumab over zoledronic acid in community hospital settings, we suspected that a significant incidence of symptomatic hypocalcemia would be evident with denosumab. Therefore, in the present research, we studied the extent of hypocalcemia with denosumab as compared to zoledronic acid in a community hospital setting and identify any risk factors associated with development of hypocalcemia.

Method
We reviewed the medical records of patients who received either denosumab (n=88) or zoledronic acid (randomly selected n=140) from June 2010 to December 2011 at Sanford Health, Fargo. The study protocol was approved by Sanford North Unit institutional review board. Patients who did not have calcium levels drawn post-injection within the one-year period were excluded from the full chart review. Final review included 151 patients who received either zoledronic acid (n=100) or denosumab (n=51). We also recorded the major indications for use of this medication (osteoporosis or SRE).

Nurse documentation was used to confirm the injection. Laboratory data (serum calcium, serum albumin, serum creatinine, estimated glomerular filtration rate (eGFR), ionized calcium and vitamin D levels where available) were obtained for a maximum of 3 times pre-injection and 3 times post-injection within a one-year period. The post-injection period up to 3 months was reviewed for any emergency room visit, office visit or phone note to obtain any adverse effects noted by patients that might be related to denosumab or zoledronic acid. All such documentation was considered an adverse drug event and was recorded.
The medication list on the electronic medical record was reviewed to note concomitant drug use including calcium, vitamin D, multivitamins, thiazides, furosemide and glucocorticoids. The problem list on the chart was used to obtain co-morbidity data from which the Charlson Morbidity Index was calculated [9].

The average of available values for laboratory data was used for the calculations with the exception of pre-injection hypocalcemia where only the value immediately before the injection was used. To calculate corrected serum calcium, the average of available albumin values for both intervals was used for both pre- and post-injection serum calcium values. Hypocalcemia is defined as a corrected serum calcium level <8.5 mg/dl.

The data are presented as means with standard deviations in parenthesis for continuous variables and percent with 95% confidence intervals in parenthesis for binomial variables. SAS 9.2 and R 2.13.1 were used for all statistical calculations.

Results

In the present study, we reviewed charts of 100 patients in the zoledronic acid group and 51 patients in the denosumab group that met the inclusion criteria. Baseline characteristics were similar between the two study groups. The mean age (standard deviation) was 73.3 (11.9) for denosumab and 73.3 (12.7) years in the zoledronic acid group.

The proportion of male patients was similar for denosumab (3.3%) and zoledronic acid (4.0%). The denosumab group had a higher Charlson Comorbidity Index median than the zoledronic acid group – 2 versus 1 respectively (P=0.023 by Wilcoxon test). The proportion of patients receiving denosumab and zoledronic acid for SRE was (4.6% and 5.3%; P=0.27) with the remainder receiving the drugs for osteoporosis.

There was no statistical difference in medication use (calcium, vitamin D, multivitamins, thiazides, furosemide, glucocorticoids and warfarin) between the denosumab and zoledronic acid group (data not presented).

Laboratory data including serum albumin, uncorrected serum calcium, corrected serum calcium, alkaline phosphatase, creatinine, eGFR, magnesium, phosphate and vitamin D levels are summarized in the Table. As expected, there was a slight, albeit statistically significant decline in alkaline phosphatase and estimated glomerular filtration rate (eGFR) between pre- and post-injection in the zoledronic acid group (Table 1).

| Variable            | Pre-Injection | Post-Injection | P   | Pre-Injection | Post-Injection | P   |
|---------------------|---------------|----------------|-----|---------------|----------------|-----|
| Albumin             | 4.0 (0.5)     | 4.0 (0.5)      | 0.78| 4.2 (0.4)     | 4.2 (0.3)      | 0.66|
| Alkaline Phosphatase| 92.3 (60.2)   | 93.6 (112.8)   | 0.92| 71.7 (28.4)   | 66.8 (24.7)    | <0.01|
| Creatinine          | 1.2 (1.0)     | 1.2 (1.1)      | 0.92| 0.8 (0.2)     | 0.9 (0.4)      | 0.06|
| eGFR                | 55.3 (8.4)    | 55.6 (8.6)     | 0.77| 58.7 (3.7)    | 57.9 (6.5)     | <0.01|
| Magnesium           | 2.1 (0.3)     | 2.0 (0.4)      | 0.50| 2.0 (0.2)     | 2.1 (0.7)      | 0.50|
| Phosphate           | 3.3 (0.8)     | 2.9 (0.7)      | 0.96| 3.5 (0.9)     | 2.9 (1.0)      | 0.50|
| Vitamin D           | 50.4 (14.6)   | 49.1 (15.4)    | 0.10| 43.4 (14.1)   | 43.8 (13.9)    | 0.79|
| Calcium (uncorrected)| 9.3 (0.6)   | 9.2 (0.7)      | 0.06| 9.4 (10.4)    | 9.3 (0.5)      | 0.23|
| Calcium (corrected) | 9.5 (0.5)     | 9.4 (0.6)      | 0.06| 9.4 (0.4)     | 9.4 (0.4)      | 0.52|

Table 1: Laboratory data by medication injected

Corrected serum calcium post-injection was not significantly different than pre-injection corrected serum calcium in either study group (Table 1). As depicted in the Figure 1, the percentage of patients developing albumin corrected hypocalcemia was higher in the patient group receiving denosumab (15.6%) as compared to zoledronic acid (8.5%), but this did not reach statistical significance (P=0.17). The frequency of hypocalcemia was statistically significant (p<0.05) following denosumab injection but not with zoledronic acid (p=0.26). One patient receiving denosumab was hospitalized with hypocalcemic tetany.

In terms of other adverse effects, 2 (3.9%) patients receiving denosumab developed paresthesia or foot swelling. In the zoledronic acid group, 8 (8%) had an adverse event including flu-like symptoms or paresthesia. There was no significant difference in the adverse effects between the two study groups.

Figure 1: Percent hypocalcemia pre- and post-injection by medication injected
Discussion

In our study, we found that there is hypocalcemia with both denosumab and zoledronic acid post-injection and roughly twice as high in the denosumab group. This is similar to previously reported studies [7,8]. The limitation of our study was that we did not have serum calcium levels in all patients within 1-2 weeks following injection when the incidence of hypocalcemia is highest. Calcium levels were obtained in patients at different time intervals following the injection, as there are no standard guidelines for the frequency and interval of laboratory monitoring. We therefore believe that actual incidence of hypocalcemia might have still been underestimated in this retrospective study with a limited number of patients.

According to most clinical trial data, denosumab is considered very safe and did not cause symptomatic hypocalcemia [3,6]. Our study also had one patient with severe hypocalcemic tetany requiring hospitalization but such severe hypocalcemia was not observed in the zoledronic acid group. The package insert for zoledronic acid recommends serum calcium levels to be >12 mg/dL prior to administration of zoledronic acid when used for SRE. No similar guideline is recommended for denosumab.

Even though rare, the possibility of life threatening hypocalcemia exists with these agents and physicians should monitor serum calcium levels closely and ensure adequate serum calcium and vitamin D levels prior to administration of denosumab.

The non-calcium adverse effects seen in our study groups were similar to those previously reported [6,8].

An additional aim of present study was to identify specific risk factors associated with denosumab/zoledronic acid induced hypocalcemia. The risk factors reported in literature that can contribute to symptomatic hypocalcemia with denosumab or zoledronic acid include: chronic kidney disease, vitamin D deficiency, hypomagnesemia, hypophosphatemia, and glucocorticoid use [10-13]. However, the small patient cohort and very low incidence of hypocalcemia in our study population limits the identification of risk factors. We also could not obtain laboratory data on all patients for vitamin D and magnesium levels, as they are not routinely measured.

In conclusion, we recommend that a prospective cohort study should be conducted in a larger community population with serum calcium level monitoring at regular intervals to determine the actual extent of hypocalcemia in patients receiving denosumab as compared to zoledronic acid. A larger study will also identify risk factors associated with hypocalcemia in community settings with use of these drugs. This will emphasize the importance of adequate calcium and vitamin D intake during therapy and will help to determine the intervals at which serum calcium should be monitored.

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