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Severe Hypocalcemia With Denosumab Among Older Female Dialysis-Dependent Patients

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IMPORTANCE Dialysis-dependent patients experience high rates of morbidity from fractures, yet little evidence is available on optimal treatment strategies. Chronic kidney disease–mineral and bone disorder is nearly universal in dialysis-dependent patients, complicating diagnosis and treatment of skeletal fragility.

OBJECTIVE To examine the incidence and comparative risk of severe hypocalcemia with denosumab compared with oral bisphosphonates among dialysis-dependent patients treated for osteoporosis.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of female dialysis-dependent Medicare patients aged 65 years or older who initiated treatment with denosumab or oral bisphosphonates from 2013 to 2020. Clinical performance measures including monthly serum calcium were obtained through linkage to the Consolidated Renal Operations in a Web-Enabled Network database.

EXPOSURES Denosumab, 60 mg, or oral bisphosphonates.

MAIN OUTCOMES AND MEASURES Severe hypocalcemia was defined as total albumin-corrected serum calcium below 7.5 mg/dL (1.88 mmol/L) or a primary hospital or emergency department hypocalcemia diagnosis (emergent care). Very severe hypocalcemia (serum calcium below 6.5 mg/dL [1.63 mmol/L] or emergent care) was also assessed. Inverse probability of treatment-weighted cumulative incidence, weighted risk differences, and weighted risk ratios were calculated during the first 12 treatment weeks.

RESULTS In the unweighted cohorts, 607 of 1523 denosumab-treated patients and 23 of 1281 oral bisphosphonate–treated patients developed severe hypocalcemia. The 12-week weighted cumulative incidence of severe hypocalcemia was 41.1% with denosumab vs 2.0% with oral bisphosphonates (weighted risk difference, 39.1% [95% CI, 36.3%-41.9%]; weighted risk ratio, 20.7 [95% CI, 13.2-41.2]). The 12-week weighted cumulative incidence of very severe hypocalcemia was also increased with denosumab (10.9%) vs oral bisphosphonates (0.4%) (weighted risk difference, 10.5% [95% CI, 8.8%-12.0%]; weighted risk ratio, 26.4 [95% CI, 9.7-449.5]).

CONCLUSIONS AND RELEVANCE Denosumab was associated with a markedly higher incidence of severe and very severe hypocalcemia in female dialysis-dependent patients aged 65 years or older compared with oral bisphosphonates. Given the complexity of diagnosing the underlying bone pathophysiology in dialysis-dependent patients, the high risk posed by denosumab in this population, and the complex strategies required to monitor and treat severe hypocalcemia, denosumab should be administered after careful patient selection and with plans for frequent monitoring.

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Supplemental content

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Osteoporosis is a common disease among postmenopausal women, characterized by a loss of bone density, weak and brittle bones, and increased risk of fracture.[1,2] Patients with advanced chronic kidney disease (CKD) have a greater risk of fractures compared with the general population.[3] In patients undergoing long-term dialysis, there is a high prevalence of CKD-mineral and bone disorder (CKD-MBD), which is characterized by abnormalities of serum phosphorus, calcium, parathyroid hormone, and vitamin D; abnormalities in bone turnover, mineralization, volume, and strength; and vascular calcification.[4] Thus, older patients who are dialysis dependent are at high risk of low bone mass attributable to primary osteoporosis, CKD-MBD, or both.[5]

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines do not endorse a particular treatment strategy for bone disease in dialysis-dependent patients but recommend that risks of treatment be weighed against the underlying bone phenotype.[4] Bone is heavily relied on as a source of calcium in patients undergoing long-term dialysis due to an impaired ability to absorb calcium from the gastrointestinal tract. Inhibition of osteoclasts by antiresorptive agents limits the body's ability to mobilize calcium from the bone. Denosumab is a much more potent inhibitor of bone turnover than other antiresorptive agents,[6] and denosumab labeling indicates that patients with advanced CKD (creatinine clearance <30 mL/min) or those undergoing dialysis are at high risk of developing hypocalcemia and recommends that prescribers consider the benefit-risk profile before administering denosumab to this population.[7]

This study thus sought to evaluate the incidence and differential risk of severe hypocalcemia in female dialysis-dependent patients treated for osteoporosis with denosumab or oral bisphosphonates.

Key Points

Question Is there a difference in risk of severe hypocalcemia among female dialysis-dependent Medicare patients treated for osteoporosis with denosumab vs oral bisphosphonates?

Findings In this cohort study of 1523 dialysis-dependent patients initiating denosumab and 1281 initiating oral bisphosphonates, the weighted cumulative incidence of severe hypocalcemia (ie, <7.5 mg/dL [1.88 mmol/L] or emergent care) at 12 weeks was 41.1% with denosumab, 60 mg, vs 2.0% with oral bisphosphonates (weighted risk difference, 39.1% [95% CI, 36.3%-41.9%]).

Meaning Treatment of older female dialysis-dependent patients with denosumab was associated with a statistically and clinically significant increased risk of severe hypocalcemia compared with oral bisphosphonates.

Methods

The Centers for Medicare & Medicaid Services require all Medicare-certified dialysis facilities to collect patient survival information and clinical performance measures for all dialysis-dependent patients, including monthly measurements of serum calcium and serum phosphorus.[8] These data are prospectively collected in the Consolidated Renal Operations in a Web-Enabled Network database (CROWNWeb) for patients undergoing long-term hemodialysis or peritoneal dialysis. More than 6000 dialysis facilities and approximately 30 kidney transplant centers have continuously contributed patient information since 2012. Data are accessible through a monthly extract containing clinical and laboratory-based measures. Prescription and comorbidity data were obtained from Medicare Part A (hospital inpatient care), Part B (outpatient medical care), and Part D (prescription drug coverage). Race and ethnicity and sex were self-reported at Medicare enrollment. Race and ethnicity categories include Asian, Black, White, and other (American Indian/Alaska Native, Hispanic, and other).

The study population was postmenopausal female Medicare patients aged 65 years or older with ongoing dialysis at Medicare-certified facilities who initiated treatment with either denosumab, 60 mg (approved dosage for osteoporosis), or an oral bisphosphonate (alendronate, risedronate, ibandronate) between August 2013 and August 2020 (new user cohort). The women had a diagnosis of osteoporosis or were receiving treatment for low bone mass after therapy with aromatase inhibitors, gonadotropin-releasing hormone agonists, or high-intensity glucocorticoids (≥60 days in prior 90 days and ≥1 day in prior week). At cohort entry, patients were required to have 15 months of continuous enrollment in Medicare Parts A, B, and D; at least 2 measurements of clinical laboratory values in the prior 3 months; and an albumin-corrected serum calcium level of 7.5 mg/dL (1.88 mmol/L) or greater at treatment initiation. Patients could not have an active day supply of the comparator study drug in the 30 days prior to treatment initiation. Use of antiresorptive agents that were not included in this study (denosumab, 120 mg; intravenous or nonstudy bisphosphonates; and anabolic agents) was not allowed in the 15 months prior to study entry. To reduce potential confounding, we excluded dialysis-dependent patients with cancers (eg, bone cancer, multiple myeloma) and other conditions (eg, benign bone neoplasm, Paget disease) that might affect serum calcium levels. The complete set of exclusion criteria is detailed in eFigure 1 in Supplement 1.

Severe hypocalcemia, the primary study outcome, was defined as an albumin-corrected total serum calcium value below 7.5 mg/dL (1.88 mmol/L)[9,10] or a primary hospital or emergency department diagnosis of hypocalcemia (emergent treatment). Very severe hypocalcemia, a subset of the primary outcome, was defined as an albumin-corrected total serum calcium measure below 6.5 mg/dL (1.63 mmol/L) or emergent hypocalcemia treatment. This approach toward defining emergent hypocalcemia treatment was previously found to have a positive predictive value of 81% to identify hypocalcemia as the primary reason for hospitalization or emergency department admission among postmenopausal women with osteoporosis enrolled in Medicare.[11] A case disposition analysis evaluated seizures, cardiac arrhythmias, and death in the 30 days following study outcomes.

Because pharmacological data indicate an acute effect of denosumab on serum calcium,[12] the analysis was limited to the first 12 weeks after treatment initiation. The primary analysis compared new initiators of denosumab with new initiators of oral bisphosphonate treatment, censoring for loss to

Table 1. Baseline Characteristics in the Weighted and Unweighted Cohorts[a]

Characteristics	Unweighted cohorts			Weighted cohort	
	Denosumab (n = 1523)	Oral bisphosphonates (n = 1281)	SMD[b]	Oral bisphosphonates (n = 1501)	SMD[b]
Age, No. (%)					
65-74	830 (54.5)	763 (59.6)	0.10	806 (53.7)	0.02
75-84	559 (36.7)	417 (32.6)	0.09	561 (37.4)	0.01
≥85	134 (8.8)	101 (7.9)	0.03	134 (8.9)	0.01
Race and ethnicity, No. (%)[c]					
Asian	82 (5.4)	89 (6.9)	0.07	82 (5.4)	0.00
Black	294 (19.3)	319 (24.9)	0.14	306 (20.4)	0.03
White	959 (63.0)	652 (50.9)	0.25	917 (61.1)	0.04
Other	188 (12.3)	221 (17.3)	0.14	196 (13.1)	0.02
Charlson comorbidity score, No. (%)[d]					
2-3	157 (10.2)	140 (10.9)	0.03	146 (9.7)	0.01
4	194 (12.7)	150 (11.7)	0.03	186 (12.4)	0.01
≥5	1172 (77.0)	991 (77.4)	0.01	1168 (77.8)	0.02
Body mass index, No. (%)[e]					
<18.5	98 (6.4)	96 (7.5)	0.04	88 (5.9)	0.02
≥18.5 to <25	599 (39.3)	460 (35.9)	0.07	572 (38.1)	0.02
≥25 to <30	401 (26.3)	376 (29.4)	0.07	420 (28.0)	0.04
≥30 to <35	240 (15.8)	196 (15.3)	0.01	231 (15.4)	0.01
≥35	185 (12.1)	153 (11.9)	0.01	189 (12.6)	0.01
Medications, No. (%)					
Vitamin D analogues	946 (62.1)	850 (66.4)	0.09	922 (61.4)	0.01
Non–calcium-based phosphate binders	833 (54.7)	711 (55.5)	0.02	834 (55.5)	0.02
Thyroid medications	513 (33.7)	377 (29.4)	0.09	503 (33.5)	0.00
Medication for type 1 diabetes	503 (33.0)	470 (36.7)	0.08	486 (32.4)	0.01
Calcium-based phosphate binders	472 (31.0)	427 (33.3)	0.05	423 (28.2)	0.06
Calcimimetics	457 (30.0)	394 (30.8)	0.02	434 (28.9)	0.02
Medications for diabetes, other drugs	273 (17.9)	251 (19.6)	0.04	267 (17.7)	0.02
Aromatase inhibitors or gonadotropin-releasing hormone agonists	136 (8.9)	41 (3.2)	0.24	121 (8.1)	0.03
Glucocorticoids, high-intensity use	72 (4.7)	42 (3.3)	0.07	71 (4.7)	0.00
Selective estrogen receptor modulators	40 (2.6)	18 (1.4)	0.09	42 (2.8)	0.01
Comorbidities, No. (%)					
Osteoporosis	1498 (98.4)	1253 (97.8)	0.04	1474 (98.2)	0.01
Hyperparathyroidism	1477 (97.0)	1246 (97.3)	0.02	1455 (97.0)	0.00
Fracture	514 (33.7)	337 (26.3)	0.16	507 (33.8)	0.00
Magnesium disorders	178 (11.7)	147 (11.5)	0.01	170 (11.4)	0.01
Dialysis covariates					
Dialysis type, No. (%)					
Hemodialysis	1400 (91.9)	1197 (93.4)	0.06	1376 (91.7)	0.01
Peritoneal dialysis	123 (8.1)	84 (6.6)	0.06	125 (8.3)	0.01

(continued)

Table 1. Baseline Characteristics in the Weighted and Unweighted Cohorts[a] (continued)

Characteristics	Unweighted cohorts			Weighted cohort	
	Denosumab (n = 1523)	Oral bisphosphonates (n = 1281)	SMD[b]	Oral bisphosphonates (n = 1501)	SMD[b]
Albumin-corrected serum calcium, median (IQR), mg/dL	9.3 (8.9-9.6)	9.2 (8.8-9.6)	0.05	9.2 (8.8-9.5)	0.01
Serum phosphorus, median (IQR), mg/dL	4.6 (4.0-5.4)	4.7 (3.9-5.4)	0.01	4.7 (3.9-5.4)	0.01
Serum albumin, median (IQR), g/dL[f]	3.7 (3.5-4.0)	3.8 (3.5-4.0)	0.02	3.8 (3.4-3.9)	0.02
Kt/V ratio, median (IQR)[g]					
Hemodialysis	1.8 (1.6-2.0)	1.8 (1.6-2.0)	0.04	1.7 (1.6-1.9)	0.01
Peritoneal dialysis	2.3 (2.0-2.8)	2.2 (1.9-2.5)	0.32	2.4 (1.9-2.7)	0.00

SI conversions: To convert calcium to millimoles per liter, multiply by 0.25; to convert phosphorus to millimoles per liter, multiply by 0.323.

[a] Demographic characteristics, medications, and medical comorbidities were assessed during the 15-month baseline period, while dialysis covariates were defined as the value at the closest time to study enrollment. A weighted oral bisphosphonate cohort was formed using the inverse probability of treatment weights approach, wherein weights were calculated from a propensity score using covariates in Table 1 and eTable 1 in Supplement 1. The denosumab group serves as the reference group for both the unweighted and weighted cohorts. See eTable 1 in Supplement 1 for a full list of baseline characteristics.

[b] Standardized mean difference (SMD) values ≥0.1 represent imbalances among cohorts.

[c] Race and ethnicity and sex were self-reported at Medicare enrollment. Race and ethnicity categories include Asian, Black, White, and other (American Indian/Alaska Native, Hispanic, and other).

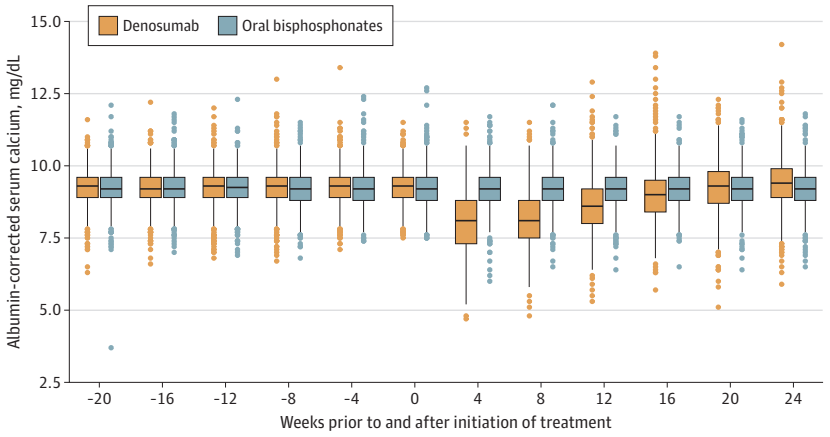
[d] A modified Charlson comorbidity score, which has a predictive value for 1-year mortality, was calculated for all patients. The score range is 0 to 24; higher scores represent a greater risk of 1-year mortality.

[e] Calculated as weight in kilograms divided by height in meters squared.

[f] Serum albumin was not included in the propensity score because adjustment for this covariate was included in the corrected serum calcium level.

[g] Kt/V is a measure of dialysis adequacy calculated using the ratio of urea clearance (K), dialysis time (t), and the volume of water in the body (V). The target ratio is ≥1.3 in hemodialysis and ≥1.7 in peritoneal dialysis.

Figure 1. Total Albumin-Corrected Serum Calcium Levels 6 Months Before and After Initiation of Denosumab or Oral Bisphosphonate Treatment



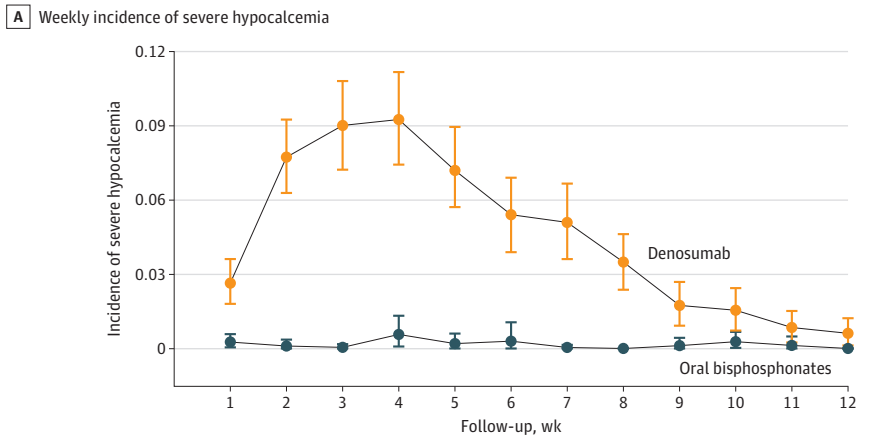
No. of patients

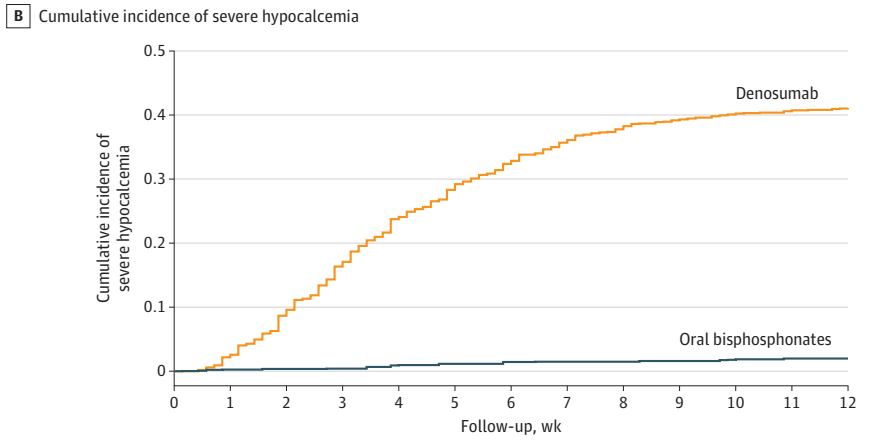
Denosumab	1280	1291	1287	1324	1347	1337	1184	1246	1188	1166	1144	1135
Oral bisphosphonates	1036	1070	1072	1099	1112	1137	1073	1038	1020	977	952	942

Median (horizontal lines) and IQR (box tops and bottoms) for total albumin-corrected serum calcium levels each month, with whiskers set at 1.5 times the IQR and circles indicating outside values. Patients with no record of a calcium measurement in a given interval were omitted from that interval. If patients had 1 or more records in the interval, the lower value was used. The oral bisphosphonate cohort was weighted using an inverse probability of treatment weights approach, wherein weights were calculated from a propensity score using covariates listed in Table 1 and eTable 1 in Supplement 1; see text for details.

follow-up, end of database, kidney transplant, and death. The inverse probability of treatment weights (IPTW) method was used to control for imbalances in baseline covariates through formation of a weighted control group, balanced on measured covariates between treatment groups.[13] The weights were calculated from a propensity score, defined as the probability of receiving denosumab given baseline covariates, which was calculated using logistic regression. The IPTW method creates a pseudopopulation bisphosphonate comparison group of patients up-weighted and down-weighted in number in which observed confounders are expected to be equally distributed across the reference and comparison groups. The denosumab group was used as the reference for propensity score weighting, which yielded the IPTW average treatment effect on the treated weights. Demographic characteristics, frailty[14] and Charlson[15] scores, medical comorbidities, medication use, health care utilization, and dialysis covariates (**Table 1**; eTable 1 in Supplement 1) were clinically selected for inclusion in the propensity score. Balance between groups was assessed by standardized mean differences, wherein covariates with standardized mean differences between groups of less than 0.1 were considered balanced.[16]

Figure 2. Severe Hypocalcemia Incidence Among Patients Treated With Denosumab and Oral Bisphosphonates





Denosumab													
No. at risk	1523	1480	1375	1246	1127	1045	983	925	890	864	844	829	819
No. with outcome	0	39	145	257	361	436	489	536	567	582	595	602	607
Oral bisphosphonates													
No. at risk	1501	1490	1484	1474	1457	1436	1423	1417	1405	1397	1383	1370	1350
No. with outcome	0	4	5	6	14	17	21	22	22	23	27	29	29

In panel A, whiskers represent 95% CIs. Severe hypocalcemia was defined as a serum calcium level below 7.5 mg/dL (1.88 mmol/L) or receipt of emergent care (primary hospital or emergency department admission diagnosis). In both plots, data are from a weighted oral bisphosphonate cohort, formed using the inverse probability of treatment weights approach, wherein weights were calculated from a propensity score using covariates listed in Table 1 and eTable 1 in Supplement 1; see text for details. A total of 6.6% of denosumab-treated patients were censored (for death, 2.4%; end of database, 2.4%; loss to follow-up, 1.1%; and kidney transplant, 0.7%); the remainder had a study outcome (39.9%) or reached the end of the 12-week study (53.7%). A total of 8% of weighted oral bisphosphonate users were censored (for death, 3.4%; end of database, 2.9%; loss to follow-up, 1.5%; and kidney transplant, 0.2%); the remainder had a study outcome (1.9%) or reached the end of the 12-week study (90.0%).

From cumulative incidence plots of severe and very severe hypocalcemia risk over time, we calculated 12-week weighted cumulative incidence (proportions), weighted risk differences, and weighted risk ratios. The 95% CIs for the risk differences and risk ratios were calculated using the bootstrap method with 1000 samples and the percentile confidence interval method. A secondary analysis used a weighted Cox proportional hazards model with robust variance estimation to compare hypocalcemia risk between denosumab and oral bisphosphonates through calculation of hazard ratios.

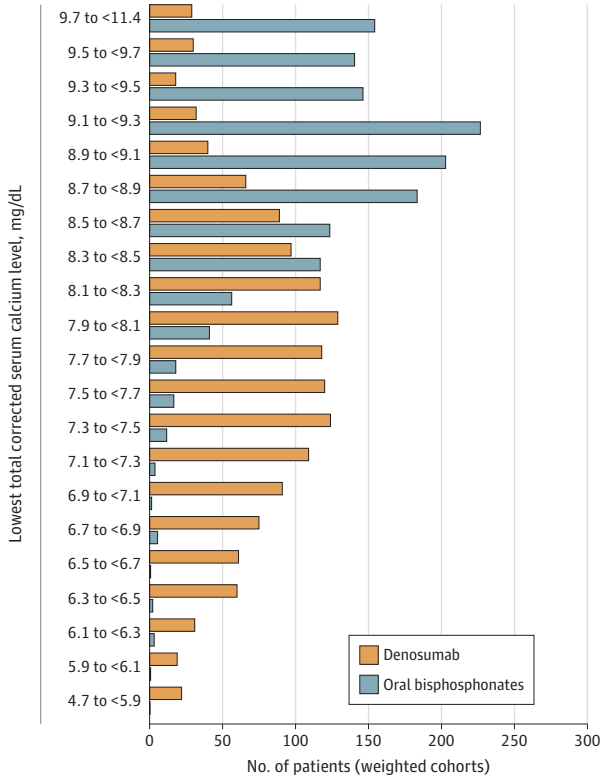
Subgroup analyses were conducted in patients aged 65 to 74 years and those aged 75 years or older, patients whose only indication for antiresorptive therapy was osteoporosis, and patients with no prior antiresorptive treatment, using the Cox model. In a post hoc analysis, death was evaluated as a competing risk using the Fine and Gray method.[17]

This study was classified as public health surveillance and was exempted from institutional review board approval and informed consent under the common rule at 45 CFR 46.102(l)(2). Analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 4.1.2 (R Foundation for Statistical Computing).

Results

The study population included 1523 women treated with denosumab and 1281 treated with oral bisphosphonates, weighted to 1501 oral bisphosphonate users in the balanced cohort. Most oral bisphosphonate users received alendronate (91.8%), with most receiving 70 mg weekly (75.7%). Nearly all denosumab (95.8%) and oral bisphosphonate (99.1%) users had no antiresorptive treatment in the prior 15 months. Denosumab users were considered exposed for the entire study time frame since they received an injection every 6 months; some oral bisphosphonate users discontinued treatment in month 2 (n = 322 [21.5%]) and month 3 (n = 90 [6.0%]). Cohort formation is shown in eFigure 1 in Supplement 1, select baseline

Figure 3. Lowest Total Albumin-Corrected Serum Calcium Level



Data shown are for 12-week follow-up and based on the weighted oral bisphosphonate cohort, formed using the inverse probability of treatment weights approach, wherein weights were calculated from a propensity score using covariates in Table 1 and eTable 1 in Supplement 1; see text for details. Some patients in the denosumab cohort (3.0% [46 of 1523]) and oral bisphosphonate cohort (3.2% [48 of 1501]) were censored or ended follow-up before a serum calcium level was recorded. All severe hypocalcemia outcomes with oral bisphosphonates (100% [29 of 29]) and nearly all severe hypocalcemia outcomes with denosumab (97.5% [592 of 607]) were based on serum calcium levels rather than hospital or emergency department diagnosis of hypocalcemia.

characteristics are provided in Table 1, and full population characteristics are shown in eTable 1 in Supplement 1. After weighting, study cohorts were well balanced for all covariates.

Mean participant age was 74.5 (SD, 6.6) years in the denosumab group and 73.8 (SD, 6.5) years in the oral bisphosphonate group.

Nearly all users in both groups had a diagnosis of osteoporosis (98.4% vs 97.8%) and markers of CKD-MBD, including hyperparathyroidism (97.0% for denosumab and 97.3% for oral bisphosphonates), vitamin D analogue use (62.1% for denosumab and 66.4% for oral bisphosphonates), and phosphate binder use (non-calcium based: 54.7% for denosumab and 55.5% for oral bisphosphonates; calcium-based: 31.0% for denosumab and 33.3% for oral bisphosphonates). Bone biopsy to confirm osteoporosis was rare (1.1% for denosumab and 1% for oral bisphosphonates). Most prescriptions for denosumab (55.7%) and oral bisphosphonates (90.7%) were from primary care clinicians. Endocrinologists and rheumatologists prescribed a larger share of denosumab (29.2%) than of oral bisphosphonates (2.3%). Nephrologists infrequently prescribed either (denosumab, 2.3%; oral bisphosphonates, 2.6%).

Median total albumin-corrected serum calcium levels were similar for denosumab (9.3 mg/dL [2.32 mmol/L]; IQR, 8.9-9.6 mg/dL [2.22-2.4 mmol/L]) and oral bisphosphonate users (9.2 mg/dL [2.3 mmol/L]; IQR, 8.8-9.6 mg/dL [2.2-2.4 mmol/L]) prior to start of therapy. After denosumab initiation, median serum calcium levels dropped sharply within the first month and remained below baseline for 4 months, while levels remained unchanged with oral bisphosphonates (**Figure 1**). Most cases of severe hypocalcemia with denosumab occurred during weeks 2 through 5, although an increased probability of severe hypocalcemia persisted through approximately posttreatment week 10 (**Figure 2**A). Serum calcium levels reached as low as 4.7 to less than 5.9 mg/dL in denosumab users (n = 22) (**Figure 3**).

In unweighted cohorts, 607 (39.9%) of 1523 denosumab-treated patients and 23 (1.8%) of 1281 oral bisphosphonate-treated patients developed severe hypocalcemia. The weighted cumulative incidence of severe hypocalcemia rose sharply within 1 week of denosumab initiation and reached 41.1% (95% CI, 38.5%-43.6%) by 12 weeks, compared with 2.0% (95% CI, 1.0%-3.0%) among oral bisphosphonate users (weighted risk difference, 39.1% [95% CI, 36.3%-41.9%]; weighted risk ratio, 20.7 [95% CI, 13.2-41.2]; weighted hazard ratio, 26.6 [95% CI, 15.8-44.9]) (**Table 2** and Figure 3).

The weighted cumulative incidence of very severe hypocalcemia in the denosumab group was 10.9% by 12 weeks, compared with 0.4% among oral bisphosphonate users (weighted risk difference, 10.5% [95% CI, 8.8%-12.0%]; weighted risk ratio, 26.4 [95% CI, 9.7-449.5]; weighted hazard ratio, 28.0 [95% CI, 8.4-93.6]) (Table 2; eFigure 2 in Supplement 1).

Denosumab-treated patients with mild to moderate hypocalcemia at treatment initiation (7.5 mg/dL to <8.5 mg/dL) had a substantially higher incidence of severe hypocalcemia (62.9% [73 of 116]) compared with those with normal baseline serum calcium (>8.5 mg/dL) (38.0% [534 of 1407]). There was no apparent difference in severe hypocalcemia incidence among denosumab users by administering clinician specialty, use of vitamin D analogues or calcimimetics (eTable 2 in Supplement 1), or type of dialysis (hemodialysis vs peritoneal) (eTable 3 in Supplement 1). Results of subgroup and sensitivity analyses were consistent with those of the main analysis (eFigure 3 in Supplement 1).

Nearly all severe hypocalcemia outcomes were identified based on albumin-corrected serum calcium levels (97.5% [592 of 607] for denosumab; 100% [29 of 29] for oral bisphosphonates) rather than emergency department or hospitalization diagnosis. Among patients with a severe hypocalcemia outcome, 10.7% (65 of 607) treated with denosumab and none treated with oral bisphosphonates required hospitalization following diagnosis. Within 30 days after onset, 5.4% (33 of 607) of denosumab-treated patients with severe hypocalcemia had a diagnosis of seizure or ventricular arrhythmia and 1.3% (8 of 607) died. There were no deaths, seizures, or cardiac arrhythmias within 30 days of severe hypocalcemia in the oral bisphosphonate cohort. Among 549 denosumab-treated patients with severe hypocalcemia who had 90 days or more of

Table 2. Outcomes for Severe and Very Severe Hypocalcemia in the Weighted Cohorts[a]

Outcomes	No. of patients	Incidence of study outcomes, No.	Weighted cumulative incidence, % (95% CI)	Weighted risk difference, % (95% CI)	Weighted risk ratio (95% CI)
Primary: severe hypocalcemia					
Denosumab	1523	607	41.1 (38.5-43.6)	39.1 (36.3-41.9)	20.7 (13.2-41.2)
Oral bisphosphonates	1501	29	2.0 (1.0-3.0)		
Secondary: very severe hypocalcemia					
Denosumab	1523	161	10.9 (9.3-12.4)	10.5 (8.8-12.0)	26.4 (9.7-449.5)
Oral bisphosphonates	1501	6	0.4 (0.0-0.9)		

[a] Severe hypocalcemia was defined as a serum calcium level below 7.5 mg/dL (1.88 mmol/L) or receipt of emergent care (primary hospital or emergency department admission diagnosis). Very severe hypocalcemia was defined as a corrected serum calcium below 6.5 mg/dL (1.63 mmol/L) or receipt of emergent care. Patient and outcome counts for the oral bisphosphonate cohort are weighted using the inverse probability of treatment weights approach, wherein weights were calculated from a propensity score using covariates in Table 1 and eTable 1 in Supplement 1. Weighted cumulative incidence, weighted risk difference, and weighted risk ratios were derived from the Kaplan-Meier plots (Figure 2B; eFigure 2 in Supplement 1), which additionally accounted for censoring by loss to follow-up, end of study, kidney transplant, and death.

subsequent Medicare enrollment, serum calcium returned to normal (>8.5 mg/dL [>2.12 mmol/L]) by day 90 in 65.8% (n = 361).

Discussion

Herein we report a markedly increased incidence of severe hypocalcemia in dialysis-dependent patients treated with denosumab compared with oral bisphosphonates, with a weighted risk difference of 39.1% (95% CI, 36.3%-41.9%) in the 12 weeks following treatment initiation. Stable serum calcium levels observed in this cohort during the 6 months prior to denosumab administration, coupled with the rapid onset and high incidence of severe hypocalcemia postadministration, suggest that this association might be causal. Patients with mild to moderate hypocalcemia at baseline were at greater risk of severe hypocalcemia with denosumab.

The early onset of severe hypocalcemia following denosumab administration aligns with the expected nadir observed in patients with normal kidney function after approximately 10 days.[7] Limited data among dialysis-dependent patients suggest that the calcium nadir is more varied, typically presenting in the first 2 weeks but up to 2 months in some patients.[12,18,19] The greatest hypocalcemia risk in our study occurred during weeks 2 through 5, with most patients having a return to baseline calcium level by month 4.

Serum calcium levels below 7.5 mg/dL (1.88 mmol/L) can result in life-threatening symptoms including seizures and cardiac arrhythmia.[9,10] These occurred in about 5% of denosumab-treated patients with severe hypocalcemia despite current product labeling that warns about hypocalcemia and treatment to regulate serum calcium during dialysis.

Concern for severe hypocalcemia in dialysis-dependent patients receiving denosumab emerged preapproval in a single-dose pharmacokinetic study.[12] This study was halted after cases of severe hypocalcemia (<7.5 mg/dL [<1.88 mmol/L]) were observed, including 2 patients requiring hospital admission.[12] The study was resumed after the protocol was amended to require calcium and vitamin D supplementation and to exclude enrollment of dialysis-dependent patients who had baseline calcitriol levels of less than 30 pg/mL (0.072 nmol/L) or intact parathyroid hormone levels of 300 pg/mL (31.8 pmol/L) or more, consistent with secondary hyperparathyroidism.[12]

Since approval, several small studies[19-29] have heightened the concern for hypocalcemia with denosumab. A meta-analysis of 55 denosumab-treated dialysis-dependent patients in 4 clinical studies reported a pooled incidence of hypocalcemia (<8.0 mg/dL [<2 mmol/L]) of 42%, with most events occurring between days 7 and 20.[18] These data are consistent with results in our much larger and more representative study.

The high proportion of patients with coexisting hyperparathyroidism, hyperphosphatemia, and vitamin D deficiency is consistent with a high prevalence of CKD-MBD in our study cohort, although all patients were being treated for a presumed diagnosis of osteoporosis. While determining the underlying bone pathophysiology in CKD patients with skeletal fragility could inform appropriate treatment strategies, bone biopsy is an invasive procedure available in only a few specialized centers and not routinely performed. Small studies have shown an improvement in bone mass in dialysis-dependent patients with CKD-MBD treated with antiresorptive drugs[20-22]; however, the effectiveness of such treatment on reduction of fracture risk has not been established in this population.[4,30,31]

Dependence on parathyroid hormone to mediate bone resorption and maintain serum calcium levels makes dialysis-dependent patients highly susceptible to hypocalcemia resulting from strong osteoclast inhibition by denosumab. Secondary hyperparathyroidism can be exacerbated by denosumab[12,21,27,28] and is a driving factor for development of high-turnover bone disease, an important risk factor for denosumab-induced hypocalcemia.[12,20-22,25,27,28] Three small studies of denosumab-treated dialysis-dependent patients with secondary hyperparathyroidism and high-turnover bone disease reported high rates of severe hypocalcemia (4 of 12 with <7.5 mg/dL [<1.88 mmol/L][20]; 8 of 24 with <8.0 mg/dL [<2 mmol/L][21]; 8 of 21 with <8.0 mg/dL [<2 mmol/L][22]), despite weekly laboratory and clinical monitoring of serum calcium and supervised administration of high-dose vitamin D and high calcium dialysate. The investigators in these studies addressed hypocalcemia and avoided serious clinical sequalae through intensive management strategies. Although nephrologists may be better positioned to select dialysis patients

appropriate for treatment, pretreat them to mitigate risk, and monitor for or treat hypocalcemia, nephrologists were responsible for prescribing only 2.3% of denosumab in our study.

This study has several strengths, including its large size and nationally representative scope with access to patient-level medical and prescription data linked to serum calcium measurements. It also has important limitations. It was not a randomized trial, and we did not have data on the decision to prescribe denosumab vs oral bisphosphonates. To address this, we used a new-user active comparator design that included a large number of covariates and applied IPTW to reduce potential for bias. We additionally did not have laboratory data for levels of vitamin D, alkaline phosphatase, or parathyroid hormone, and monthly measurements of total serum calcium did not allow a more precise calculation of time to calcium nadir. Over-the-counter supplementation with calcium and vitamin D could not be measured, and adherence to supplementation recommendations could not be assessed. Finally, the study may have reduced generalizability in settings where practices relating to selection and care of patients receiving denosumab differ from those in the United States.

Conclusions

In conclusion, this study identified a higher incidence of severe and very severe hypocalcemia after denosumab initiation compared with oral bisphosphonates in dialysis-dependent patients treated for osteoporosis. Risk was greater among patients with mild to moderate hypocalcemia at baseline. Given the complexity of diagnosing the underlying bone pathophysiology in dialysis-dependent patients, the high risk posed by denosumab in this population, and the complex strategies required to monitor and treat severe hypocalcemia, denosumab should be administered after careful patient selection and with plans for frequent monitoring.

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