Main Title:

Severe Symptomatic Hypocalcemia after Denosumab Administration in an End-Stage Renal Disease Patient on Peritoneal Dialysis with Secondary Hyperparathyroidism – A Different Mechanism for Hungry Bone Syndrome.

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Short Title: Hypocalcemia after Denosumab

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Source of Funding: N/A. Potential Conflicts of Interest: LAJ - Gambro's Speaker Bureau; MT – Employer: Fresenius Medical Care, Consultancy Agreement: Pannonpharma Kft, Hungary

Words count – Abstract: 250; Body of article: 1,788

Abstract

We report the first case of severe, symptomatic hypocalcemia after denosumab (RANKL inhibitor) treatment in a peritoneal dialysis patient with secondary hyperparathyroidism and osteoporosis.

58 year-old Caucasian female on chronic ambulatory peritoneal dialysis for four years secondary to polycystic kidney disease. Laboratory studies revealed: albumin-corrected calcium 9.0 mg/dL, phosphorus 5 mg/dL, alkaline phosphatase 58 U/L [normal, 40-105], albumin 3.4 gm/dL [normal, 3.6-5.4] and intact PTH 315 pg/mL [normal, 40-72]. She had a markedly osteoporotic stature and a DEXA scan revealed bone mineral density T-scores ranging between -3.3 and -7.4 Standard Deviation below for her age and sex. She had failed conventional medical treatment, including *per os* calcium, monthly ergocalciferol (50,000 units/month), activated vitamin-D analog and renal-failure adjusted alendronate (70 mg twice a month). She was started on subcutaneous denosumab 60 mg every 6 months. After her first dose, she developed a progressive drop of calcium, phosphorus, bicarbonate and magnesium, in spite of massive escalation of bioactive vitamin-D analog and calcium supplementation. Hypocalcemia nadired at 6.3 mg/dL with symptomatic tetany, requiring a brief hospitalization approximately 7 weeks after denosumab treatment. Her elevated PTH rose further transiently (647 pg/mL), along with ALP (123 U/L). Bone-mineral parameters normalized approximately 3 month after denosumab administration. The observed phenomenon resembled, the phenotype of "hungry bone syndrome" observed after surgical parathyroidectomy.

Conclusion. Treatment decisions based on bone densitometry results alone are not transposable between patients with or without end-stage renal disease. Denosumab may lead to critical hypocalcemia in dialysis patients and further aggravate existing secondary hyperparathyroidism.

Key words: denosumab, end-stage renal disease, hypocalcemia, osteoporosis, RANK ligand inhibitor, tetany

Introduction

Bisphosphonates bind bone mineral and are absorbed by mature osteoclasts, inducing osteoclast apoptosis and suppressing resorption(1, 2). Due to the potential renal toxicity of bisphosphonates, there has been some interest in the use of denosumab, a RANK Ligand inhibitor for treatment of osteoporosis in patients with renal impairment. Until recently, Denosumab, as per the manufacturer's instructions, did not require dosage adjustments for renal impairment(3). Published experience of the use of denosumab in end-stage renal disease (ESRD) is, however, very scant. One preliminary study of 8 hemodialysis patients(4) and another case report have raised concerns about severe hypocalcemia in hemodialysis patients(5). We report the first case of severe symptomatic hypocalcemia secondary to denosumab in a peritoneal dialysis-dependent patient with secondary hyperparathyroidism.

Presentation of Case

Our index patient was a 58-year-old Caucasian female with end-stage renal disease (ESRD) secondary to polycystic kidney, who had been on chronic ambulatory peritoneal dialysis (CAPD) for 4 years. Due to a markedly osteoporotic stature with a dorsal “hump”, a dual-energy x-ray absorptiometry (DEXA) scan was obtained in August of 2011, revealing markedly decreased bone mineral density ranging from -3.3 to -7.2 Standard Deviation below for her age and sex in multiple locations (left femoral neck and spine). She denied a prior history of osteoporosis or any fracture. Except for continued tobacco abuse, she denied risk factors such as steroid medications, seizure medications or a family history of osteoporosis. She had been on a vitamin D supplement 50,000 units once a month and was previously on over-the counter calcium-carbonate as phosphorus binder; however, she developed transient hypercalcemia and calcium carbonate was discontinued. She was placed on alendronate (Fosamax®) which she had been taking without any difficulty. However, she noted progressive loss of height over the ensuing months and her severe osteoporosis preventing her from renal transplant listing.

Co-morbid issues associated with her ESRD included secondary hyperparathyroidism and hyperphosphatemia, renal anemia with functional iron deficiency and chronic hypoalbuminemia and hypokalemia associated with peritoneal dialysis. Other co-morbidities included prior cerebrovascular accident with no residual deficit, well-controlled hypertension, allergic rhinitis, chronic anxiety, history of colonic polyps and arterio-venous malformations and vitamin-D deficiency requiring replacement. For chronic metabolic acidosis, she was taking potassium-citrate on a long-term basis.

In terms of ESRD, she had done reasonably well on a CAPD regimen of 2 liters x 4 exchanges with 1.5% dextrose solution. Return volumes were always satisfactory, resulting in a net ultrafiltration of 300-800 mL per exchange. Comprehensive dialysis flow sheets revealed excellent Kt/V's between 2.2-2.8 per week but a progressive loss of creatinine clearance over the years, most recently 52 L/week/1.73 m^2. Her residual urine output was very limited (30-40 mL/day) and contributed little to her overall clearance.

Laboratory studies at baseline revealed: albumin-corrected calcium 9.0 mg/dL, phosphorus 5 mg/dL, alkaline phosphatase 58 U/L [normal, 40-105], albumin 3.4 gm/dL [normal, 3.6-5.4] and intact parathyroid hormone 315 pg/mL [normal, 40-72]. The 25-hydroxy vitamin-D level was normal at 31.3 ng/ml [normal, 20-100], 1,25 di-hydroxy Vitamin D was 25 pg/mL [normal, 18-78]. Four years earlier, serum protein and urine electrophoresis revealed only non-selective proteinuria and no evidence of multiple myeloma. Baseline medications included doxercalciferol (2.5 mcg twice weekly), sevelamer (2400 mg TID with meals and 1600 mg at bedtime), ergocalciferol (50,000 Units once a month) and alendronate (70 mg twice a month). Rheumatology consultants recommended to discontinue her alendronate and to start denosumab every 6 months. The first dose was given on 06/22/12 along with instructions to take daily over-the-counter 500 mg calcium carbonate. After her first dose, she developed a progressive drop of calcium, phosphorus, bicarbonate and magnesium, in spite of massive escalation of bioactive vitamin-D analog and calcium supplementation (calcium acetate 2001 mg three times daily, calcium carbonate 2250 mg at bedtime, doxercalciferol 2.5 mcg daily) and increased

calcium content of peritoneal fluid to 3.0 mEq/L. Hypocalcemia nadired at 6.3 mg/dL with symptomatic tetany requiring a brief hospitalization locally approximately 7 weeks after denosumab treatment. As expected, PTH rose transiently during this period (647 pg/mL), along with ALP (123 U/L). After a short period of transient hypercalcemia, bone-mineral parameters, including calcium, phosphorus and ALP normalized approximately 3 month after denosumab administration. Incidentally, she had an episode of back pain after sudden jerking movements of her extremities and torso in July 2012 leading to an x-ray investigation (8/14/12) showing right superior and inferior pubic rami fractures which demonstrated healing on follow-up X-rays.

Discussion

Denosumab is the first Federal Drug Administration (FDA) approved RANK Ligand inhibitor. As Prolia® (Thousand Oaks, CA, USA), it was initially approved in June 2010 for treatment of postmenopausal osteoporosis with high risk of fractures. This approval was based on a three-year, randomized, double-blind, placebo-controlled trial of 7,808 osteoporotic postmenopausal women ages 60 to 91 years (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months or FREEDOM Study), in which denosumab reduced the incidence of vertebral, non-vertebral, and hip fractures(6). Indications since then have been expanded to include increasing bone mass in patients at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer (Approval September 2011), and to increase bone mass in men with osteoporosis at high risk for fracture (Approval September 2012). As Xgeva®, Denosumab is also approved for prevention of skeletal-related events in patients with bone metastases from solid tumors with the exception of Multiple Myeloma (Approval November 2010).

Osteoclast differentiation factor, also called receptor activator of nuclear factor (NF-κB) ligand (RANKL), stimulates the differentiation of osteoclast progenitors into osteoclasts. Osteoprotegerin acts as a natural soluble decoy receptor to bind RANKL and thus, reducing RANKL binding to RANK and

reducing bone resorption. Denosumab is a full length human monoclonal antibody of IgG2 subtype mimicking the action of natural osteoprotegerin by binding to and inhibiting RANKL. It exhibits a nonlinear, dose dependent pharmacokinetics after subcutaneous injection, with levels peaking in 7-21 days(7). As expected for an IgG antibody, it is not cleared by the kidneys and, therefore, does not require dosage adjustments for renal impairment(4). Denosumab administration results in rapid and sustained decrease for markers of bone resorption; in one study, an 85% reduction in serum C-telopeptide of type I collagen (a bone resorption marker reflecting osteoclast activity) was seen in 3 days, with a peak reduction in one month(3). Therefore, this potent and long lasting effect on bone remodeling raises the concerns for hypocalcemia. This was clinically noted in the FREEDOM trial in which within one month, 1.7% of subjects from the drug arm experienced calcium values below 8.5 mg/dl as opposed to 0.4% in the placebo arm(6, 8). It should be noted that in the FREEDOM Trial, only 73 women had a calculated creatinine clearance 15 to 29 mL/min and none had end-stage renal dysfunction (< 15 mL/min) and, therefore, it was underpowered to study the hypocalcemic effects of denosumab in severe CKD or terminal renal failure(9). In patients with normal kidney function, nadir in serum calcium is noted on day 10(3). This hypocalcemic effect appears to be more pronounced in patients with renal insufficiency. In the FREEDOM Extension study of 4,550 subjects, a more marked reduction in serum calcium was noted in subjects with renal insufficiency: -5.5% reduction in mean serum calcium in subjects with creatinine clearance < 30 mL/min vs. -3.1% in subjects with creatinine clearance ≥ 30 mL/min at approximately day 10(3, 10). In another study of 55 patients with various degrees of renal impairment, severe and persistent hypocalcemia was noted in subjects with severe CKD (GFR <30 mL/min/1.73 m^2), which was especially profound with kidney failure requiring hemodialysis. 5 out of 8 dialysis dependent patient developed hypocalcemia (serum calcium < 8 mg/dL) and calcium dropped below 7.5 mg/dL in 2 of them(4). Additionally, McCormick et al. also recently reported a case of severe hypocalcemia with denosumab in a hemodialysis patient(5). Interestingly, a recent case report mentioned successful treatment of immobilization-related

hypercalcaemia with denosumab in a patient with advanced renal insufficiency(11). In a boy with fibrous dysplasia, denosumab did not impair healing of a femoral fracture that occurred while on treatment during which, similar to our case presented here, secondary hyperparathyroidism developed(12).

Clinical experience thus far suggests that denosumab can result in a rapid and sustained reduction in serum calcium in the presence of severe renal insufficiency or renal failure. This effect may be more pronounced in patients with a history of secondary hyperparathyroidism, perhaps as a function of a larger osteoblast mass in these patients. Inhibition of osteoclastic activity by denosumab may result in excess unopposed osteoblastic activity and resultant severe sustained hypocalcemia, analogous to what we observe as “hungry bone syndrome” after surgical parathyroidectomy(13, 14). This sustained hypocalcemia can also (further) elevate PTH and aggravate existing secondary hyperparathyroidism. Of note, our patient with existing secondary hyperparathyroidism had previously been treated with a bisphosphonate (Fosamax) before denosumab had been administered while 1,25-dihydroxy vitamin D and 25-OH vitamin D levels were within normal range, suggesting an additive effect of both antiresorptive agents. Additionally, RANKL is an important part of immune regulation and denosumab might increase susceptibility to infections. This is of special concern in ESRD patients as they already suffer from immune dysfunction with infections accounting for 20% of the total mortality(15). Our patient had PTH in the target range, normal calcium and vitamin D levels at baseline, and was already receiving calcium supplementation and activated vitamin D analog for secondary hyperparathyroidism. While hypocalcemia was expected, the magnitude and the length of the process were certainly surprising to us. Of note, Health Canada placed a hypocalcemia alert on denosumab in June of 2012 (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/_2012/xgeva_pc-cp-eng.php). Additionally, the manufacturer (Amgen) also issued additional warning in the US in September of 2012 (http://www.proliahcp.com/pdf/dear_healthcare_professional_letter.pdf), including indicating the risk of severe hypocalcemia.

Currently, we do not have any current guidelines about e.g. adjusting the initial dose of denosumab during the first treatments. Nonetheless, simply avoiding this medication from the therapeutic armamentarium may not be the best policy. The very fact that our patient developed such a severe degree of hypocalcemia may serve as a predictor of an excellent potential for bone mineralization and successful future outcomes for bone integrity - yet another issue in need of study for ESRD patients. On the other hand, whether denosumab has any role in treating hypercalcemia in dialysis patients is unclear at this time.

Conclusion

Treatment decisions based on bone densitometry results alone are not transposable between patients with or without end-stage renal disease. An powerful anabolic agent such as denosumab may lead to critical hypocalcemia in dialysis patients and further aggravate existing secondary hyperparathyroidism. Additional research is needed to identify the highest risk patients and effective strategies to minimize this dangerous side effect.

Acknowledgement.

We wish to thank Ilena S. Agarwal, who has worked closely with the first author and who critically read the manuscript in every draft and helped prepare it for publication.

Figures and Legends

Figure 1.

Calcium, adjusted Calcium and Phosphorus changes after Denosumab administration

Table 1.

Changes of Bone-Mineral Metabolism Parameters after Denosumab Administration

Abbreviations: IU=International Unit; iPTH=intact parathyroid hormon

Competing Interests

Source of Funding: N/A. Potential Conflicts of Interest: LAJ – member of Gambro's Speaker Bureau; MT – Employer: Fresenius Medical Care; Consultancy Agreement: Pannonpharma Kft, Hungary

Authors' contributions

This work was carried out in collaboration between all authors. Author MA and TF designed and written the case report. Authors MA and VE collected the data. Author MA, TF and KAC managed the literature searches. Authors LAJ, ÉC, KAC and MT further edited the manuscript and provided critical commentary. All authors read and approved the final manuscript.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Ethical Approval

This case report is not an animal experiment or experimental study. Informed consent was obtained from the patient.

Figure 1.

Calcium, adjusted Calcium and Phosphorus changes after Denosumab administration

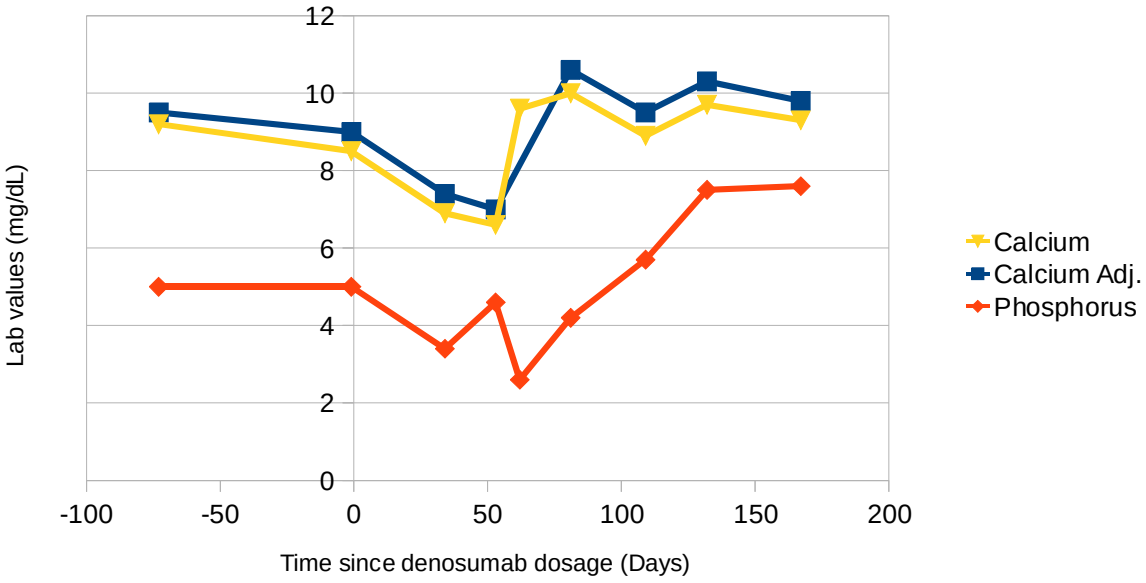

Table 1.

Changes of Bone-Mineral Metabolism Parameters after Denosumab Administration

Date (Days Since Denosumab dosage)	**04/10/12 (-73)**	**06/21/12 (-1)**	**07/26/12 (34)**	**08/14/12 (53)**	**08/23/12 (62)**	**09/11/12 (81)**	**10/09/12 (109)**	**11/01/12 (132)**	**12/06/12 (167)**	**Ref. Range**
Calcium	9.2	8.5	6.9	6.6	9.6	10.0	8.9	9.7	9.3	8.2-10.1 mg /dL
Calcium Adj.	9.5	9.0	7.4	7.0		10.6	9.5	10.3	9.8	8.2-10.1 mg/dL
Phosphorus	5.0	5.0	3.4	4.6	2.6	4.2	5.7	7.5	7.6	2.5-5.0 mg/dL
Alkaline Phosphatase	58		85	123		122	62	50	43	40-105 IU/L
iPTH	315		647				117			14-72 pg/mL

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