

Severe Hypocalcemia Following a Single Denosumab Injection

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Receptor activator of nuclear factor- κ B ligand (RANKL) plays a central role in mediating bone resorption through osteoclast development and activity. After menopause, increased RANKL causes increased bone resorption and bone loss, which can lead to osteoporosis, a condition characterized by the weakening of bone strength and an increased risk of fractures [1].

Denosumab, sold under the trade name Prolia[®] (Amgen Inc., Thousand Oaks, CA, USA), is a fully human monoclonal antibody that links with high specificity to human RANKL, thereby diminishing osteoclast number and activity and lowering bone resorption. Prolia has been approved by the U.S. Food and Drug Administration for use as a second-line treatment in postmenopausal women with a risk of osteoporosis. It has also been approved for the prevention of skeletal-related events in patients with bone metastases from solid tumors, and is sold under the trade name XGEVA[®] (Amgen Inc., Thousand Oaks, CA, USA). The recommended dose for Prolia is 60 mg subcutaneously every 6 months, whereas for XGEVA the dose is 120 mg subcutaneously every 4 weeks. In light of the high likelihood of developing hypocalcemia and considering the mechanism of action described previously, the recommended dosage is 1000 mg oral calcium and 400 IU vitamin D daily, along with Prolia [1]. In the 3 year, placebo-controlled FREEDOM study [2], administration of 60 mg Prolia subcutaneously every 6 months was proven

to be efficient in reducing the risk of new vertebral, hip, and non-vertebral fractures in a number of postmenopausal osteoporotic women. In view of the knowledge to date, we present two patients with mild and moderate renal failure and severe hypocalcemia, which followed treatment by a single dose of Prolia. The patients were hospitalized during 2 consecutive months, which is not consistent with the rarity of such events, as described so far.

PATIENT DESCRIPTION

CASE NUMBER 1

An 84 year old woman was transferred from a hematology outpatient clinic to an internal medicine department because of hypocalcemia. This patient had no past history of hypocalcemia.

Six weeks before being hospitalized, she received an initial, single subcutaneous 60 mg dose of denosumab for treatment of osteoporosis. Three months earlier the patient received her last dose of risedronate sodium, completing 3 years of therapy. She had a long-standing history of chronic lymphocytic leukemia. She was not taking elemental calcium or vitamin D before treatment with Prolia. The patient's serum calcium was 9.3 mg/dl, serum creatinine was 0.55 mg/dl, creatinine clearance was 68 ml/min (Cockcroft-Gault equation), serum albumin level was 4.1 g/dl, serum phosphorus was 3.7 mg/dl, serum alkaline phosphatase was 139 IU/L (normal 30–120 IU/L), and serum vitamin D was 13.1 nmol/L. Two weeks later, the patient received one single injection of 60 mg denosumab. Results of serum calcium, beginning 2 weeks following denosumab, are shown in Table 1. She was hospitalized

for hypocalcemia because of fatigue and malaise, when serum calcium was 5.5 mg/dl. No paresthesia or tetany was noted. However, the QT interval was mildly prolonged as shown in an electrocardiograph. There were no changes in other biochemical data. Treatment included 1 mcg alpha D3 (alfacalcidol) tablets twice daily, and 1200 mg calcium carbonate tablets twice daily for 5 days. At the end of the treatment, total serum calcium rose to 8.4 mg/dl [Table 1]. No further denosumab therapy was planned.

CASE NUMBER 2

An 84 year old woman was referred to the emergency room with confusion, dizziness, and agitation. She was checked by a psychiatrist and 5 mg of haloperidol intramuscular treatment was recommended. A computerized tomography scan of the head showed signs of chronic brain ischemia. Past medical history was notable for chronic renal failure with creatinine levels between 1.4 mg/dl and 1.6 mg/dl. She had long-standing hypertension and nephrotic syndrome for the last 2 years. Neither kidney biopsy nor nephrology follow-up were performed. Seven years prior a pacemaker was implanted due to second degree Mobitz II atrioventricular block. Chvostek's sign was positive. Her medical treatment included raloxifene chloride, omeprazole, cinnarizine, and atorvastatin. Laboratory blood tests revealed a low serum total calcium level of 4.3 mg/dl. Creatinine was 1.76 mg/dl, phosphorus 2 mg/dl, albumin 3.79 g/dl, alkaline phosphatase 135 U/l, magnesium 1.38 mg/dl, and creatinine clearance 35 ml/min (Cockcroft-Gault equation). Parathyroid hormone (PTH) levels were elevated (1260 pg/ml) and the vitamin D

Table 1. Calcium and phosphorus in two patients who were treated with denosumab

	Case Number 1		Case Number 2	
	Calcium (mg/dl)	Phosphorus (mg/dl)	Calcium (mg/dl)	Phosphorus (mg/dl)
Before Prolia®	9.3	3.7	8.72	
A single injection of Prolia				
2 weeks after Prolia	7.2	2.3		
6 weeks after Prolia, patient hospitalized	5.5	3.2	4.3	2.2
Alfacalcidol and calcium carbonate treatment				
After 5 days of hospitalization	8.4	2.2	6.3	2.8
After 10 days of hospitalization			7.5	2.4

level was 5 nmol/l. Urinary 24 hour calcium was 6.75 mg and 24 hour protein was 4068 mg. Electrocardiography was normal. Past history revealed that 6 weeks before admission she was seen by her family physician. Treatment of daily 400 UI vitamin D drops was recommended and after that she received, for the first time, a single subcutaneous dose of 60 mg of denosumab for treatment of osteoporosis. Prior to denosumab administration serum calcium level was 8.72 mg/dl. Serum level of vitamin D was checked 4 months earlier and was less than 10 nmol/L. No other blood tests were ordered between denosumab injection and her admission to the hospital. Treatment of hypocalcemia during admission was with calcium gluconate infusions on the first day. After that a protocol of 600 mg of calcium carbonate 3 times per day, 1 mcg daily of alpha D3 (alfacalcidol), and 300 mg of magnesium citrate daily was instituted for 10 days. At the end of the treatment total calcium level was 8.4 mg/dl, serum magnesium 1.94 mg/dl, and serum creatinine 1.41 mg/dl [Table 1].

COMMENT

These cases focus on a dangerous unique phenomenon: severe hypocalcemia 6 weeks post-therapy in two 84 year old female patients with serum creatinine values considered appropriate for denosumab administration. Both patients had a vitamin D deficiency. Neither patient received calcium supplementation, while only one received a sub-therapeutic dose of vitamin D supplementation. Patients with low

vitamin D levels can develop severe hypocalcemia that can be resistant to treatment. They might not always show symptoms of hypocalcemia until the serum calcium falls to dangerously low levels. In the FREEDOM study [2] 1827 women received Prolia for 6 years. There were no reports of severe hypocalcemia in the denosumab group and three events (0.1%) in the placebo group. Calcium levels below 8.0 mg/dl occurred in four subjects in the denosumab group and five in the placebo group. Renal failure was not an exclusion criteria. In the DIRECT study [3], 810 Japanese women who received 60 mg of Prolia subcutaneously every 6 months with daily supplements of calcium and vitamin D for 2 years were enrolled for 1 additional year of therapy. Evidence of 2.0 mg/dl of serum creatinine or greater was an exclusion criterion. Only two cases of mild hypocalcemia were confirmed and none resulted or led to discontinuation of denosumab or study withdrawal [3]. According to the Cockcroft-Gault equation, our patients had chronic kidney (CKD) disease stage 2 and stage 3. In these stages denosumab administration results in rapid reduction of bone turnover, and serum denosumab levels are not affected by the degree of renal damage. One study [4] suggested that high-bone-turnover patients with a high PTH level are prone to denosumab-related hypocalcemia due to a phenomenon akin to hungry bone syndrome, which can be attributed to the state after parathyroidectomy. The endogenous supply of calcium from bone is rapidly reduced, but deposition of mineral calcium and phosphate into a new matrix remains elevated. In the

time required for new osteoid formation to adequately mineralize, hypocalcemia may result unless calcium is appropriately supplemented. Block and colleagues [4] noticed a broad range of alkaline phosphatase and PTH values in hypocalcemic patients post-denosumab, which suggests that not only high-bone-turnover patients but also those with adynamic bones, can develop hypocalcemia. For the patients with CKD 4–5 who developed hypocalcemia post-denosumab, the median time to serum calcium nadir was 21 days, and the median time to correction of hypocalcemia was 71 days. It was observed that vitamin D supplementation may be a less effective supportive therapy in these patients with a creatinine clearance below 70 ml/min as its conversion to its active form from 1-alpha-hydroxylation of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol is progressively impaired. The use of calcitriol may be advantageous in combination with denosumab in at least two different experimental settings: in cancer patients with a creatinine clearance less than 30 ml/min and in those with mild to moderate kidney failure with recurrent hypocalcemia [5]. The fact that our patients received activated vitamin D from the first day of admission can explain the relatively rapid correction of hypocalcemia.

CONCLUSIONS

In conclusion, we presented the cases of two elderly patients with osteoporosis, who experienced renal failure, one mild and one moderate. They each developed severe hypocalcemia 6 weeks after being administered a single 60 mg dose of Prolia. It is crucial to ask patients presenting with hypocalcemia about previous therapies or injections. At first it was not obvious that the patients had received Prolia. Supplementation of activated vitamin D and checking both vitamin and serum calcium levels prior to administration of this drug are essential for preventing this adverse effect. Monitoring serum calcium levels after drug administration is a critical issue, regardless of the patient's basal serum calcium. We suggest that the rarity concept

attributed to this drug's unique toxicity, be re-examined, both in general and especially in CKD patients.

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Capsule

Light- and dark-zone death dynamics

Germinal centers (GCs) are areas within lymphoid organs where mature B cells expand and differentiate during normal immune responses. GCs are separated into two anatomic compartments: the dark zone, where B cells divide and undergo somatic hypermutation, and the light zone, where they are selected for affinity-enhancing mutations after interacting with T follicular helper cells. Mayer and colleagues studied apoptosis reporter mice and found that both GC

zones experience very high rates of apoptosis. However, the underlying mechanisms were distinct and micro-anatomically segregated. Light-zone B cells underwent apoptosis by default unless they were rescued by positive selection. In contrast, apoptotic dark-zone B cells were highly enriched among cells with genes damaged by random antibody-gene mutations.

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Capsule

Co-occurrence and characteristics of patients with axial spondyloarthritis who meet criteria for fibromyalgia

Macfarlane and colleagues tried to estimate the proportion of patients with axial spondyloarthritis (SpA) in a UK national biologics registry who met criteria for fibromyalgia, and to delineate the characteristics of these patients. Of the patients registered in the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS), 1504 (68% male) were eligible for the current analysis, of whom 311 (20.7%) met the 2011 research criteria for fibromyalgia. Prevalence of fibromyalgia was similar between patients who fulfilled the modified New York criteria for ankylosing spondylitis (AS) (19.7%) and those who fulfilled Assessment of SpondyloArthritis international Society (ASAS) imaging criteria but not the modified New York criteria (25.2%); however, among those who fulfilled only the ASAS clinical criteria, the prevalence of fibromyalgia was lower (9.5%). Patients who

met fibromyalgia criteria reported significantly worse disease activity, function, global severity scores, and quality of life, and were more likely to have moderate or severe levels of mood disorder and clinically important fatigue. Patients who met fibromyalgia criteria reported experiencing work impairment around half their working time. Meeting fibromyalgia criteria was not related to elevated C-reactive protein levels or most extraspinal manifestations, but was associated with a higher likelihood of having received biologic therapy. Developing management approaches that would address the significant unmet clinical needs of the 1 in 5 patients with axial SpA who meet criteria for fibromyalgia should be a research priority.

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Eitan Israeli

“The doctrine which, from the very first origin of religious dissensions, has been held by bigots of all sects, when condensed into a few words and stripped of rhetorical disguise, is simply this: I am in the right, and you are in the wrong. When you are the stronger, you ought to tolerate me, for it is your duty to tolerate truth; but when I am the stronger, I shall persecute you, for it is my duty to persecute error”

Sir Thomas James Babington Macaulay, Baron of Rothley generally known as Baron Macaulay, (1800–1859), British historian and Whig politician