

Dramatic Elevation in Parathyroid Hormone after Denosumab Administration in a Woman with Scleroderma

Keywords: Prolia; Denosumab; Hypocalcemia; PTH; Hyperparathyroidism; Scleroderma

Abstract

Denosumab (Prolia), an injectable human monoclonal antibody with affinity for nuclear factor-kappa ligand (RANKL), is approved for the treatment of osteoporosis in postmenopausal women and men at high risk for fracture, or patients who have failed or are intolerant of other treatments. There have been case reports of denosumab leading to elevated parathyroid hormone (PTH) among patients with severe renal impairment, defined as creatinine clearances under 30 mL/min or on dialysis, which is the level at which the manufacturer suggests monitoring for hypocalcemia. We report a case of a marked increase in PTH in a woman with suspected malabsorption due to scleroderma, without severe renal impairment, whose intractable diarrhea limited her treatment options.

Introduction

Denosumab (Prolia), an injectable human monoclonal antibody with affinity for nuclear factor-kappa ligand (RANKL), is approved for the treatment of osteoporosis in postmenopausal women and men at high risk for fracture. RANKL inhibitors, such as denosumab, are distinct from their bisphosphonate counterparts in that they reversibly inhibit osteoclast activity and bone turnover [1]. Among those prescribed denosumab are patients who do not tolerate the adverse gastrointestinal effects of bisphosphonates.

Hypocalcemia has been reported as an adverse effect of denosumab. In addition, denosumab administration has been linked to elevations in parathyroid hormone (PTH) among patients with severe renal impairment, defined as creatinine clearances (CrCl) under 30 mL/min or on dialysis, which is the level at which the manufacturer suggests monitoring for hypocalcemia [2,3]. We report a case of a marked increase in PTH in a woman with scleroderma without severe renal impairment, whose intractable diarrhea limited her treatment options.

Case Report

An 85-year-old woman with Scl-70 positive scleroderma, who was receiving azathioprine and prednisone, was found on dual energy X-ray absorptiometry (DEXA) to have osteopenia (AP spine T-score -2.0). During the same period, she began to develop intermittent diarrhea, which appeared to be a manifestation of worsening scleroderma. Given her DEXA findings, chronic corticosteroid use, and gastrointestinal symptoms, there was interest in avoidance of oral bisphosphonates. She received denosumab as well as 2,000 IU cholecalciferol and 1,000 mg calcium carbonate daily. One month

before administration of denosumab, biochemical testing revealed a normal intact PTH (iPTH) (31 pg/mL; normal range 14 - 64 pg/mL), serum calcium (9.0 mg/dL; normal range 8.6 - 10.4 mg/dL), albumin (3.6 g/dL; normal range 3.6 - 5.1 g/dL; low 25-hydroxyvitamin D (25[OH]D; 27.1 ng/ml, normal range 30 - 100 ng/mL), with moderate renal impairment with a CrCl of 47 mL/min, calculated by the Cockcroft-Gault equation.

Subsequently, the patient reported nausea, vomiting, and the sensation of esophageal dysmotility. Given the progression of these symptoms and 12-pound weight loss over two months, the patient presented to the hospital for feeding tube placement. However, she had difficulty tolerating tube feeds, suffering from continued nausea, vomiting and diarrhea. Simultaneously, she required frequent electrolyte repletion including almost daily high-dose intravenous phosphorous, raising concern for re-feeding syndrome. However, despite normalization of other electrolytes including magnesium, she remained hypophosphatemic. At that time, testing revealed iPTH of 1135 pg/mL, calcium 6.4 mg/dL (corrected: 8.1 mg/dL), albumin 1.9 g/dL, phosphorus 1.6 mg/dL, 25(OH)D 14.3 ng/ml. Given her pronounced hyperparathyroidism in the setting of low serum calcium and 25(OH)D, treatment was initiated with 50,000 U ergocalciferol three times per week for five doses, followed by weekly dosing. After three days of high-dose vitamin D supplementation, iPTH was 579 pg/ml, calcium 7.2 mg/dL (albumin level unavailable), and phosphorus 2.4 mg/dL; after one week, iPTH was 170 pg/mL, calcium 8.1 mg/dL, albumin 2.3 g/dL, and phosphorus 2.3 mg/dL; after 12 days, iPTH was 78 pg/mL, calcium 9 mg/dL, albumin 3.5 g/dL, and phosphorus 3.8 mg/dL. Concurrently, she experienced resolution of diarrhea and complete tolerance of oral intake after discontinuation



Nicholas Streicher¹, Tania Ahuja^{2*} and Catherine Constable³

¹Department of Neurology, University of Iowa Hospitals and Clinics, 2007 Roy Carver Pavilion 200 Hawkins Drive, Iowa City, IA, 52242, United States

²Clinical Pharmacy Manager, Internal Medicine & Anticoagulation, Clinical Pharmacotherapy Specialist, Internal Medicine, New York University Langone Medical Center, 550 First Avenue, New York, NY 10016, United States

³Department of Medicine, New York University Langone Medical Center, 550 First Avenue, New York, NY 10016, United States

*Address for Correspondence

Tania Ahuja, Clinical Pharmacy Manager, Internal Medicine & Anticoagulation, Clinical Pharmacotherapy Specialist, Internal Medicine, New York University Langone Medical Center, 550 First Avenue, New York, NY 10016, United States, E-mail: tania.ahuja@nyumc.org

Submission: 03 June 2017

Accepted: 03 July 2017

Published: 11 July 2017

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of azathioprine and treatment with rifaximin for presumed small bowel overgrowth from scleroderma.

Discussion

Hypocalcemia is a known adverse effect of denosumab administration, particularly among patients with renal impairment. In a retrospective study aimed at identifying risk factors for hypocalcemia associated with denosumab, in both univariate and multivariate logistic regression analyses, creatinine clearance of less than 50 mL/min was an independent risk factor for denosumab-associated hypocalcemia [4]. Although the pharmacokinetics and pharmacodynamics of denosumab appear to be unchanged in patients with various degrees of renal impairment, the potential for hypocalcemia appears greater as the severity of renal impairment is increased [5]. In the FREEDOM trial, however, which included patients with up to stage 5 chronic kidney disease (GFR<15 ml/min), hypocalcemia remained rare at up to 8-year follow-up [6,7].

In the post-approval period, marked elevations in serum PTH levels in patients with CrCl < 30 ml/min have been noted [2]. In animal and human models, Makras and colleagues found that denosumab causes a dose-dependent increase in PTH, thought to be compensatory to transient hypocalcemia [8]. Severe hypocalcemia with a concomitant dramatic increase in serum PTH has also been reported in patients with malabsorption due to Crohn's Disease taking denosumab [9].

Calcium and vitamin D supplementation in patients taking denosumab remains an area of uncertainty. In phase III clinical trials of denosumab, vitamin D supplementation was given to study subjects according to baseline levels of 25(OH)D: 400 IU daily if screening 25(OH)D concentration was >20 ng/mL, or 800 IU daily if screening 25(OH)D was between 12 and 20 ng/mL. The manufacturer of denosumab recommends all patients receive 1000 mg calcium and at least 400 IU daily vitamin D, consistent with the standardized approach in the FREEDOM trial, which notably excluded patients with vitamin D deficiency (<30 nmol/ml, or 12 mg/mol) [7].

In osteoporotic postmenopausal women treated with denosumab, Makras and colleagues found a statistically significant decrease in serum corrected calcium and increase in PTH in patients supplemented with 1 g calcium carbonate and 800 IU cholecalciferol daily, which was not seen in patients supplemented with 2 g calcium carbonate and 1600 IU cholecalciferol daily. In the low-dose group, the increase in PTH persisted at 6 months, despite normalization of serum corrected calcium levels. Baseline GFR, serum phosphate, 25(OH)D, and corrected calcium were similar in the two groups [8].

While case reports to date have supported the manufacturer's threshold of severe renal impairment for monitoring for hypocalcemia, defined as CrCl of 30 ml/min or on dialysis, our patient had only moderate renal impairment with a CrCl of 47 mL/min. Of note, our patient also likely suffered from intestinal malabsorption due to scleroderma. A malabsorption syndrome may have impaired her absorption of supplemental calcium and vitamin D, which can offset the hypocalcemic effect of denosumab, as demonstrated by Makras and colleagues [8]. In addition, malabsorption from gastrointestinal manifestations of scleroderma may lead to hypomagnesemia which can decrease the release of PTH and induce skeletal resistance to

PTH along with severe hypocalcemia. However, our patient had magnesium levels within the normal range. While the presence of a malabsorption syndrome should raise suspicion for concomitant hypocalcemia, which is a contraindication to denosumab, notably, our patient had normal corrected calcium one month prior to receiving denosumab (9.3 mg/dL).

The dramatic elevation in iPTH in this case calls attention to the unique effect of denosumab on mineral metabolism and the potential for serious metabolic derangements in patients with underlying risk factors for hypocalcemia, such as scleroderma. By contrast, hyperparathyroidism due to vitamin D deficiency alone - even severe, symptomatic deficiency-typically causes mild elevations in serum iPTH [10-12]. Thus, although suboptimal vitamin D status alone was unlikely to be the primary cause of her profoundly elevated iPTH, it likely contributed to the derangement, as supported by the normalization of PTH levels with high dose vitamin D supplementation.

Based on the Makras and colleagues' data, the manufacturer's recommended supplementation doses of 1000 mg/400IU of calcium/vitamin D may be insufficient to prevent hypocalcemia and rises in PTH in patients with normal renal function and normal oral intake and absorption [8]. Our patient developed hypocalcemia and hyperparathyroidism despite concurrent therapy with 2000 IU vitamin D and 1000 mg calcium carbonate. She likely required particularly high doses of vitamin D to correct her hypocalcemia and hyperparathyroidism due to multiple reasons including malabsorption from the gastrointestinal involvement of her scleroderma, corticosteroid use, moderate renal impairment, and borderline low 25-hydroxyvitamin D prior to initiation of denosumab.

This case demonstrates increasing evidence that patients with moderate renal impairment may be at heightened risk of hyperparathyroidism due to denosumab. While denosumab, in this case, was preferred over bisphosphonates to avoid worsening gastrointestinal symptoms, these symptoms were likely indicative of an underlying malabsorptive pathology that increased her risk of the adverse effect described. We suggest close monitoring of calcium, magnesium, phosphorus, and 25(OH)D levels prior to and during treatment with denosumab in patients with suspected malabsorption or corticosteroid use with moderate to severe renal impairment.

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