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Case Report

Safety of Denosumab in Dialysis Patients on Calcium and Vitamin D Supplements

Asad Ullah[1], K. Abdulnabi[1], A. Khalil[1], J. Alexander[1], P. Pai[1], V. Mishra[2]

Departments of [1]Nephrology and [2]Clinical Biochemistry and Metabolic Medicine, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, United Kingdom

Introduction

Osteoporosis and chronic kidney disease (CKD) are common comorbidities in older population.[1,2] Severe CKD [estimate glomerular filtrate rate (eGFR) <30 mL/min/1.73 m^2] is characterized by spectrum of bone metabolic disorders, which varies from high bone turnover including mild secondary hyperparathyroidism, osteitis fibrosa to low bone turnover including osteomalacia, and adynamic bone diseases. Osteoporosis is characterized by increased osteoclastic bone resorption activity resulting in high bone turnover or impaired bone remodeling. Bone mineral density which confirms the diagnosis of osteoporosis in CKD Stage 1–3 can be decreased in severe CKD due to number of other bone pathologies. The markers of bone turnover such as C-terminal telopeptide (CTx), parathormone (PTH), and alkaline phosphatase (ALP) are helpful in assessing the bone turnover in severe CKD.[3] The potential risk of osteoporosis if left untreated, is the bone fragility fractures, which increases the morbidity and mortality in these patients.[4] However, treatment options for osteoporosis in severe CKD (eGFR <30 mL/min/1.73 m^2) and dialysis are limited. The administration of antiresorptive therapy may worsen the low bone turnover and exacerbate the hyperparathyroidism in severe CKD patients. This particularly applies to patients on dialysis who have high incidence of adynamic bone.[5]

Bisphosphonates, commonly used in postmenopausal osteoporosis, is not recommended in patients with severe renal impairment due to its direct nephrotoxic effect,[6] risks of adynamic bone disease, and prolonged retention in the bone.[3] Denosumab (DN) has been approved since 2010 for the treatment of postmenopausal osteoporosis. DN is a fully human monoclonal antibody to the receptor activator of nuclear factor-kB ligand (RANKL). By blocking the binding of RANKL to RANK, DN decreases the number and activity of osteoclasts thus decreasing bone resorption.[7] In a study of postmenopausal women with osteoporosis over 36 months,

Correspondence to:

Dr. Asad Ullah,
Department of Nephrology,
Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool,
United Kingdom.
E-mail: drasadullah99@hotmail.com

treatment with DN led to a significant increase in the bone mineral density of the spine, hip and the radius, and decreased incidence of new vertebral, nonvertebral, and hip fractures compared to placebo.[8] Moreover, treatment efficacy of DN is neither affected by kidney function nor it affects the kidney function.[9] None-theless, the safety of DN in patients with eGFR <30 mL/min/1.73 m^2 is not clear. Recent MHRA alert[10] has warned against the development of severe hypocalcemia following DN administration in patients with severe CKD/dialysis. Further recommending that severe CKD patients should have adequate intake of calcium and Vitamin D and normal serum calcium levels before administration of DN therapy to prevent hypocalcemia.

We present four severe CKD cases on dialysis that developed severe hypocalcemia following DN therapy in spite of being on calcium and Vitamin D supplements for a long time and having normal serum calcium levels before DN therapy.

Case Report

We present four dialysis patients; one peritoneal dialysis (PD), three hemodialysis (HD), who were diagnosed with osteoporosis according to the WHO criteria by dual energy X-ray absorptiometry scan and two patients had a history of bone fragility fractures. They were treated with DN 60 mg subcutaneously and developed significant hypocalcemia following therapy. All these patients were on high-dose Vitamin D supplement/calcium for more than six months before DN was administered.

Case 1

A 77-year-old man was on PD for 14 years and suffered from metastatic prostate cancer. He was on one-alfacalcidol 1 µg alternate days, 1 g calcium a day, and cinacalcet 60 mg daily. Six weeks after receiving the DN therapy, he presented to casualty with a week history of tingling, numbness, and muscles cramps. Blood results showed severe hypocalcemia. He was treated with intravenous calcium gluconate, cinacalcet was stopped, one-alfacalcidol was increased to 1 µg daily, and calcium was increased to 3 g daily. Serum calcium normalized after eight weeks. He died few weeks after hypocalcemia episode.

Case 2

A 50-year-old woman was on maintenance HD. She had parathyroidectomy for tertiary hyperparathyroidism. However, PTH started to rise again after a few years. She was on one-alfacalcidol 1.5 µg alternate days; 750 mg of calcium daily and lanthanum carbonate 1.5 g three times daily. One week after DN therapy, the patient developed symptomatic hypocalcemia with cognitive impairment and prolonged QT interval requiring hospitalization. She was treated with intravenous calcium gluconate and one-alfacalcidol was changed to calcitriol 1 µg daily, oral calcium was increased to 1.5 gm daily, and the lanthanum carbonate was reduced to 500 mg three times daily. Serum calcium levels stabilized after seven weeks.

Case 3

A 72-year-old female was on home HD. She was on one-alfacalcidol 0.5 µg daily and sevelamer 1.6 g three times daily. After two weeks of DN therapy, she presented with asymptomatic hypocalcemia, which was managed by increasing the one-alfacalcidol dose to 1 µg daily and commenced on calcium 1 g daily. The hypocalcemia was corrected after approximately eight weeks.

Case 4

A 64-year-old female was on maintenance HD. She was on cinacalcet 30 mg daily, alucap 475 mg four times daily, and one-alfacalcidol 1 µg daily. She developed asymptomatic hypocalcemia four weeks after DN. One-alfacalcidol dose was increased to 2 µg daily but continued with the same dose of cinacalcet and alucap.

Serum biochemistry before administration of DN (pre)

Bone turnover markers; serum ALP (except one patient) and serum carboxy-terminal collagen crosslinks (CTX) were increased in all

Table 1. Biochemical markers of bone turnover in blood before (pre) and after (post) DN.

Normal range	Corrected calcium (2.2–2.6 mmol/L)		Phosphate (0.8–1.50 mmol/L)		ALP (30–130 U/L)		PTH (1.1–6.9 pmol/L)		CTX (0.1–0.5 µg/L)		25(OH)D (>75 nmol/L)
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Case 1	2.32	1.58	1.49	1.41	189	101	16.3	NA	1.18	NA	NA
Case 2	2.65	1.98	1.74	1.13	98	92	105	87.5	2.90	2.25	30.3
Case 3	2.58	1.98	0.78	0.45	323	227	67.9	179	4.37	1.07	40.5
Case 4	2.33	1.97	0.98	0.62	336	196	54.8	108.8	5.82	0.58	68.7

ALP: Alkaline phosphatase, PTH: Parathyroid hormone, CTX: C-terminal telopeptide, 25(OH)D: 25 hydroxyvitamin D, NA: Not available, DN: Denosumab.

patients, suggesting high bone turnover. Serum PTH was more than nine times the upper limit of reference range in three patients. Serum total 25-hydroxy (OH) Vitamin D levels were <75 nmmol/L in three patients (in one patient levels were not available). All the patients had serum corrected calcium within the reference range (Table 1).

Serum biochemistry after administration of DN (post)

After DN therapy, all four patients developed severe hypocalcemia (serum corrected calcium <2.0 mmol/L). Bone turnover markers showed reduction following DN therapy (Table 1).

Discussion

We report four dialysis patients who presented with severe hypocalcemia after administration of 60 mg of DN. The patients were on calcium and Vitamin D supplements and had normal-corrected serum calcium levels before administration of DN. It took approximately eight weeks for our patients to recover from severe hypocalcemia. A previous case report has reported severe hypocalcemia in a dialysis patient who received 60 mg subcutaneous DN therapy but was not on Vitamin D supplements.[11]

Three patients (Vitamin D levels were not available in one patient) had low Vitamin D (<75 nmmol/L) status and had severe hyperparathyroidism (more than nine times the upper reference range for PTH). Hence, patients presented with the severe hypocalcemia following DN and also took a longer time to recover from hypocalcemia. This suggests that repletion of Vitamin D stores before DN administration would have prevented hypocalcemia in these patients. Block et al[12] did not observe hypocalcemia in subjects with severe CKD who were receiving calcium (1 g) and Vitamin D supplements daily. This study[12] however excluded subjects with severe CKD/dialysis patients with low Vitamin D level (<75 nmol/L) or severe secondary hyperparathyroidism. Our study patients were on high dose of one-alfacalcidol (0.5–1.5 µg daily) before and after DN therapy. Nevertheless, despite intake of Vitamin D supplements, they had insufficient Vitamin D status. It has been strongly recommended that patients with severe CKD/dialysis should have adequate calcium and Vitamin D supplementation before and after DN therapy to prevent hypocalcemia.[10] Thus, it is prudent to assess the adequacy of calcium and Vitamin D status of the patient who is on Vitamin D supplements. Besides low Vitamin D status, two of our patients were on cinacalcet, which may be an additional risk for hypocalcemia following DN therapy.

Uncontrolled hyperparathyroidism in severe CKD/dialysis patients leads to high bone turnover. Our patients except one had inappropriately high PTH resulting into an increased CTX (marker of bone resorption) and ALP (bone formation marker) consistent with a high bone turnover disease (Table 1). DN being an antiresorptive agent reduced the bone turnover in our patients (Table 1) as reflected by reduced CTx and ALP. Thus, DN remodels the bone, which requires calcium for mineralization of new osteoid tissue. The

administration of DN in patients with high bone turnover creates a situation similar to "hungry bone syndrome"[12] leading to a sudden influx of calcium into the bone necessary for bone mineralization and remodeling. Severe hyperparathyroidism aggravated by low Vitamin D status may be responsible for severe hypocalcemia in our patients following DN therapy. Conversely, DN-induced hypocalcemia in dialysis patients can occur in the absence of inappropriate high PTH, which could be due to concomitant Vitamin D deficiency.[11] Hence, monitoring of Vitamin D status along with serum calcium is essential in dialysis patients before administration of DN therapy.

The data regarding the efficacy of DN in patients with severe CKD/ dialysis are very limited. A *post hoc* analysis of the FREEDOM trial could not show a statistically significant reduction in fractures as there were too few patients with Stage 4 CKD.[9] Besides this, there are no data on DN efficacy in CKD Stage 5 or in dialysis patients. The KDIGO working group[3] has recommended a bone biopsy before initiating treatment with antiresorptive agent in severe CKD/dialysis. Currently, there is no consensus on the management of osteoporosis in severe CKD/dialysis, which is largely opinion based.

Our case reports suggest that safety of DN in dialysis patients is determined not only by normal serum corrected calcium levels but also depends on adequate Vitamin D status. Severe hyperparathyroidism in the presence of Vitamin D supplements should initiate Vitamin D testing in a dialysis patient, as it might suggest inadequate Vitamin D supplementation.

To conclude, safety of DN can be improved in dialysis patients by ensuring the correction of serum corrected calcium and vitamin D levels before administration of DN. Adequate calcium and Vitamin D supplementation should be maintained before and after DN therapy. Calcimimetics should be stopped before DN therapy and restarted once serum calcium stabilizes. Long-term effects of DN on clinical outcomes in dialysis patients are yet to be explored.

Conflict of interest: None declared.

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