CASE REPORT

Denosumab for treatment of immobilization-related hypercalcemia in a patient with end-stage renal disease

Atsuko Uehara¹ · Masahiko Yazawa¹ · Atsumi Kawata¹ · Rina Hachisuka¹ · Yugo Shibagaki¹

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Abstract The efficacy and safety of denosumab for the treatment of immobilization-related hypercalcemia in end-stage renal disease remain uncertain. We describe the case of a hemodialysis patient with immobilization-related hypercalcemia who was successfully treated with denosumab. A 79-year-old man admitted for hemodialysis after sustaining an acute kidney injury developed immobilization-related hypercalcemia due to the impairment resulting from an acute myocardial infarction, acute heart failure, and catheter-related bloodstream infection. After admission, the patient's corrected serum calcium rose to 12.9 from 8.8 mg/dL. A bisphosphonate (alendronate) was administered, but it was ineffective. Subsequently, treatment with denosumab proved to be effective and his corrected serum calcium level declined to 9.3 mg/dL within 1 week. Hypocalcemia, which is an adverse effect of denosumab, was prevented using active vitamin D and calcium supplementation, and his calcium level stabilized. Thus, our case demonstrates that denosumab is a viable therapeutic option for dialysis patients experiencing immobilization-related hypercalcemia.

Keywords Hypercalcemia · Immobilization · End-stage renal disease · Denosumab

Introduction

Immobilization-related hypercalcemia occurs when osteoclastic bone resorption exceeds the rate of osteoblastic bone formation causing an imbalance in the bone remodeling process [1]. Although it occurs primarily in children because of their high rate of bone turnover, renal insufficiency increases the risk of immobilization-related hypercalcemia [2].

Denosumab is a novel agent registered for the treatment of osteoporosis and malignancy-induced hypercalcemia. It is a monoclonal antibody against the receptor activator of nuclear factor- κ B ligand (RANKL) that inhibits osteoclast activity [3]. Denosumab's effectiveness and safety for the treatment of immobilization-related hypercalcemia in patients with advanced renal failure managed without hemodialysis have been reported but remain uncertain in those requiring hemodialysis (HD) [4, 5]. We describe the case of a hemodialysis patient with immobilization-related hypercalcemia successfully treated with denosumab.

Case report

The patient was a 79-year-old man with a medical history of chronic kidney disease attributable to diabetes mellitus. Five months prior to admission, he was diagnosed with gastric cancer, and based on the patient's contrast-enhanced computed tomography examination gastric resection was recommended. However, he subsequently developed acute kidney injury requiring dialysis due to contrast-induced nephropathy. He was transferred to our hospital for HD and treatment of gastric cancer.

His medical history was also significant for hypertension, cerebral infarction, and peripheral artery disease.

✉ Atsuko Uehara
atsuko_mori@hotmail.com

¹ Division of Nephrology and Hypertension, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1, Sugao, Miyamae-ku, Kawasaki-shi, Kanagawa 216-8511, Japan

Medications administered in the past included clopidogrel, nicorandil, bisoprolol, irbesartan, amlodipine, doxazosin, furosemide, sodium bicarbonate, lansoprazole, and rebamipide.

HD was initiated, but soon after admission, the patient experienced an acute myocardial infarction, acute heart failure, and catheter-related bloodstream infection. He became physically incapacitated, and due to the severity of his illness, the gastric surgery was canceled.

At the time of admission, his total calcium concentration (uncorrected for albumin) was 7.2 mg/dL, his corrected serum calcium level was 8.8 mg/dL, and his serum phosphorus concentration was 9.1 mg/dL. We used Payne's formula to correct the calcium concentration using albumin measurements as follows:

Corrected calcium = total calcium + (4.0 – albumin). Although a different formula for correction [total calcium + (4.0 – albumin) * 0.8] is used in Europe and the U.S., Payne's formula is commonly used in Japan for its simplicity [6].

As seen in Fig. 1, the patient's corrected serum calcium level gradually increased after admission. By hospital day 21, he had developed significant hypercalcemia, general fatigue, appetite loss, constipation, and pruritus. Although the patient did not receive medications or supplements that could cause an increase in serum calcium concentration (such as calcium, vitamin D, or thiazide diuretics), his ionized calcium was 3.28 mEq/L (normal, 1.02–1.37 mEq/L) and corrected serum calcium was 12.9 mg/dL. His intact parathyroid hormone was 9 pg/mL, and 1.25 (OH) Vitamin D3 was 11 pg/mL reflecting appropriate suppression considering his high calcium level. His serum protein electrophoresis was unremarkable. The results of thyroid function studies were normal, and adrenal insufficiency was ruled out by an adrenocorticotrophic hormone stimulation test. His parathyroid-related protein concentration was undetectable, and humoral hypercalcemia of malignancy was unlikely. Bone scintigraphy was performed and revealed no bone metastases. His lumbar spine *T* score was –1.8 indicating osteopenia. His serum bone alkaline phosphatase, a bone

Fig. 1 Corrected serum calcium and inorganic phosphorus levels over the course of hospitalization. The period of immobilization and various treatments for hypercalcemia are shown. Serum osteocalcin (a bone resorption marker) and serum type 1 collagen cross-linked N-telopeptide and tartrate-resistant acid phosphatase-5b, (bone for-

mation markers) before (*left*) and after (*right*) denosumab treatment are shown below the *graph*. *PO* per os, *SQ* subcutaneously, *Ca* calcium, *OC* osteocalcin, *NTX* type 1 collagen cross-linked N-telopeptide, *TRACP5b* tartrate-resistant acid phosphatase-5b

Table 1 Published case reports of denosumab use in immobilization-related hypercalcemia with chronic kidney disease without HD

	Age (years)	CKD stage	cCa before denosumab administration	cCa after denosumab administration	Time point of low Ca (post dose)	Ca/Vit. D supplementation
de Baus and Boer [5]	19	4	12.1 mg/dL	7.2 mg/dL	1 week	CaCO ₃ /calciferol and alfacalcidol
Booth and Hays [10]	79	4	12.6 mg/dL	9.9 mg/dL	1 week	Not reported

CKD chronic kidney disease, cCa corrected serum calcium, Ca calcium, CaCO₃ calcium carbonate, HD hemodialysis, Vit. D vitamin D

formation marker, was slightly elevated and both serum type-1 collagen cross-linked N-telopeptide and tartrate-resistant acid phosphatase-5b, which are bone resorption markers, were significantly elevated. These bone turnover markers showed an imbalance of bone formation and resorption, with a prevalence of bone resorption.

Based on this clinical information, immobilization-related hypercalcemia was diagnosed. The patient's calcium concentrations did not decrease even though he was undergoing HD with dialysate containing 2.75 mEq/L of calcium three times per week. He was treated with 35 mg/week of alendronate orally for 2 weeks, which did not result in any improvement. Subsequently, we treated the patient with 60 mg of denosumab subcutaneously. His total calcium level decreased to 11.6 from 12.9 mg/dL within 24 h after denosumab administration. His corrected serum calcium level reached 9.3 mg/dL 1 week later, and we initiated daily treatment with calcium carbonate (1.5 g) and alfacalcidol (0.5 µg) to prevent hypocalcemia. With this dose of calcium and active vitamin D supplementation, his calcium level finally stabilized in the 9.0–10.0 mg/dL range towards the final week of his 8-week hospitalization. With this treatment, his general condition, appetite, and bowel function recovered, and the patient was discharged from the hospital on day 51.

Discussion

The present case highlights two clinical issues. First, denosumab is effective for the treatment of immobilization-related hypercalcemia in patients with end-stage renal disease (ESRD). Second, active vitamin D and calcium supplementation is useful for preventing hypocalcemia, an adverse effect of denosumab, especially when it is used in patients with advanced kidney dysfunction.

Hypercalcemia in dialysis patients is most commonly due to the excessive use of calcium-based binders or the use of vitamin D receptor agonists followed by malignancy-associated hypercalcemia. However, when drug- and malignancy-induced hypercalcemia are excluded,

immobilization-related hypercalcemia should be considered. To date, only a few reports have described immobilization-related hypercalcemia in patients on maintenance dialysis therapy [2]. However, dialysis patients are predisposed to immobilization due to a high risk of metabolic and nutritional derangements and cardiovascular events. Thus, immobilization-related hypercalcemia may be a more common cause of hypercalcemia in this population than is currently recognized. Further, mobilization is the only treatment for this condition; however, dialysis patients are restricted to bed during HD treatments, and hemodynamic instability post-treatment makes it difficult for these patients to participate in rehabilitation [7].

Aggressive intravenous hydration, which is an option for treatment of hypercalcemia, can be unsafe for patients with ESRD with oliguria or anuria. Bisphosphonate and HD using a low-calcium dialysate are symptomatic treatment options for immobilization-related hypercalcemia in the setting of ESRD. A low-calcium dialysate was unavailable in our hospital. In the current case, we began treatment with alendronate, but it was ineffective, possibly because its antiresorptive potency was insufficient. The limitations of bisphosphonates are: (1) they are excreted by the kidney, (2) few data are available on their long-term toxicities, and (3) maximal effects are not seen for several days [8, 9]. On the other hand, as Table 1 shows, the efficacy and safety of denosumab for the treatment of immobilization-related hypercalcemia in chronic kidney disease patients managed without HD has been reported [5, 10]. However, to our knowledge, this is the first report describing the use of denosumab to treat a patient with ESRD undergoing HD.

Bisphosphonates and denosumab inhibit osteoclast-mediated bone resorption. Using these drugs for immobilization-related hypercalcemia is reasonable because the main etiological factor for hypercalcemia is the rate of bone resorption exceeding that of bone formation. The advantages of denosumab over bisphosphonates include: (1) rapid onset of the therapeutic effect, (2) longer duration of the effect, and (3) no need for dose adjustment based on the glomerular filtration rate. Another benefit of denosumab is that it can be subcutaneously injected, which

offers therapeutic efficacy in patients with gastrointestinal disease who, like our patient, cannot take or absorb medication orally. Further, the effect of denosumab lasts several months which benefits patients by eliminating the need for frequent clinic visits.

Hypocalcemia is the most concerning adverse effect of denosumab, especially in chronic kidney disease patients [11]. The possible mechanisms include: active vitamin D deficiency, hungry bone syndrome with hyperdynamic bone disease, concomitant use of cinacalcet, increased osteoprotegerin activity, and RANKL removal in HD patients [12]. To prevent denosumab-induced hypocalcemia, supplementation of active vitamin D and calcium is reasonable for chronic kidney disease patients.

In conclusion, our case demonstrated that denosumab is effective for treating immobilization-related hypercalcemia in patients undergoing HD even when a bisphosphonate is not effective or contraindicated, and possible hypocalcemia can be prevented using active vitamin D and calcium supplementation.

Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

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Informed consent Informed consent was obtained from the patient in the case report.

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