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Case Report

Severe hypocalcemia after denosumab administration in a patient with chronic kidney disease: a case report

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Abstract

Patients with altered kidney function are at increased risk of hypocalcemia after denosumab administration. There is however a small number of studies and case reports describing hypocalcemia refractory to treatment. We describe a case of severe hypocalcemia, after the administration of three doses of denosumab, in a young patient with lupus nephritis under corticosteroid coverage and osteopenia. However, more studies are needed in order to extract a safe conclusion about the factors that contribute to the development of severe hypocalcemia in this group of patients.

Keywords: Bones, Calcium, Denosumab, Hypocalcemia

Introduction

Patients with chronic kidney disease (CKD) are at increased risk of fractures, with the risk rising as the kidney function declines. Multiple epidemiological studies[1,2] confirm this trend. Moreover, patients with CKD face worse clinical outcomes when they sustain a fragility fracture compared to people with normal kidney function[3,4]. RANKL is considered as an essential mediator of osteoclast differentiation, activation and survival, therefore a key factor for bone resorption. Denosumab, is a human monoclonal RANKL antibody that prevents the activation of osteoclasts via the inhibition of RANKL[5]. An interesting point is that denosumab is cleared by the reticuloendothelial system; therefore, it can be used in patients with chronic kidney disease without dose adjustment[6]. However, in the group of patients with advanced CKD (i.e., estimated glomerular filtration rate eGFR<30 ml/min) there are limited clinical studies. Although the FREEDOM and ADAMO trials were not focused on patients with CKD, a vast number of participants that were included had stage 1-3 disease defined by eGFR. As far as ADAMO trial was concerned, a significantly higher BMD compared to placebo at all sites (vertebral/hip) and greater reduction in bone turnover was noticed[7]. FREEDOM trial of denosumab in post-menopausal women included patients with eGFR as low as 15 ml/min/1.73m^2. The conclusion extracted was that the incidence of vertebral fractures was lower in women under denosumab versus placebo for all stages of CKD. An interesting fact was that the difference was not statistically important in patients with CKD stage 4[8]. However, hypocalcemia is a risk when using denosumab in patients with CKD, especially when there is advanced renal disease and it is an interesting fact that there is not a large number of studies that investigate the predisposing factors that can lead to severe hypocalcemia refractory to treatment.

Case Presentation

A 38-year-old woman, with a history of Systemic Lupus Erythematosus (SLE), lupus nephritis stage III/IV (under corticosteroid coverage), osteonecrosis of the left hip, osteopenia and amenorrhea since 2013, was admitted in the

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Table 1. DXA measurements of spine.

	BMD (20/09/2021)	BMD (20/04/2022)	Z-score (20/09/2021)	Z-score (22/04/2022)
L1	1.044	0.960	-0.7	-1.4
L2	1.058	1.036	-1.1	-1.4
L3	1.147	1.053	-0.4	-1.2
L4	1.095	1.082	-0.8	-1
L1-L4	1.089	1.039	-0.7	-1.2
L2-L4	1.101	1.069	-0.8	-1.1

Table 2. Drug dosage during follow-up.

Follow up (months after discharge)	Calcium-corrected for albumin (mg/dl)	Dose of calcium carbonate/ cholecalciferol *per os* daily (mg/IU)	Dose of alfacalcidol *per os* daily (mcg)	Dose of cholecalciferol *per os* daily (IU)
1st/first week	9.7	4000/3200	4	1200
2nd/first month	8.4	3000/2400	3.5	1200
3rd/second month	7.8	2000/1600	3	1200
4th/fifth month	7.5	2000/1600	2	1200
5th/sixth month	7.8	2000/1600	1	1200
6th/seventh month	7.7	1000/800	0.5	1200

nephrology department of our institute due to symptomatic hypocalcemia (corrected Calcium: 4.5 mg/dl). Concerning hypocalcemia, the patient presented to the emergency department, 19 days after the last dose of denosumab, with circumoral numbness and negative Chvostek/Trousseau signs. The laboratory work-up showed the following: Creatinine: 2.3 mg/dl, GFR (MDRD): 22.6 ml/min/1.73m^2, potassium: 4.8 mmo/l, calcium: 4.6 mg/dl, albumin: 4.1 g/dl, magnesium: 2.3 mg/dl, phosphate: 4 mg/dl, ALP: 60 U/l, PTH: 504.2 pg/ml, 25-hydroxy-vitamin D: 5.4 ng/ml. The ECG revealed a QT prolongation. The patient's drug history included prednisolone, belimumab and mycophenolate. Moreover, because of the long-term intake of corticosteroids therapeutically for SLE, the patient was treated with bisphosphonates and specifically zoledronic acid was administered iv for 2 years consecutively. The patient's renal function was normal before the beginning of therapy with bisphosphonates. Taking into account the clinical fracture risk assessment, osteonecrosis of the left hip, in combination with the decline in Bone Mineral Density and the dose of glucocorticoids that the patient was receiving (7.5 mg of prednisolone daily for more than 6 months), it was decided by the medical team that was in charge of the patient at that time, to proceed with a second dose of zoledronic acid. Ever since, the regimen changed to denosumab in the beginning of 2021 and the reason for this was a decline in renal function, as it was reported by the medical history of the patient. We should take into account that this regimen is not without risks in patients with CKD, but in our case an individualized approach was considered. Therefore, calcium carbonate *per os* combined with cholecalciferol was given one month before the beginning of treatment with denosumab (even though cholecalciferol level was in a low-normal range), in a dose of 2000 mg daily combined with 1600 IU of cholecalciferol. Bone mass densitometry measurements of the spine are presented in Table 1, where it is worth noting that there is a decline of the bone mass, even though the patient was on therapy with denosumab, for several months. The patient received in total 3 doses. At this point it is important to emphasize that the level of corrected for albumin calcium in the venous blood was in the normal range after the first and the second dose of denosumab administration, and it was only after the third subcutaneous administration of the drug that severe hypocalcemia was noticed. This was the first time that the patient attended the emergency department of our hospital and subsequently was admitted in the nephrology department.

Specifically, as it was described earlier, 19 days after the last dose of denosumab the patient attended the hospital with severe hypocalcemia (laboratory results and clinical signs are discussed previously) that proved to be refractory to treatment, therefore she was admitted to the hospital. She received a total of 15 g of calcium carbonate *per os* (during her 5-day hospitalization), 50 g of intravenous

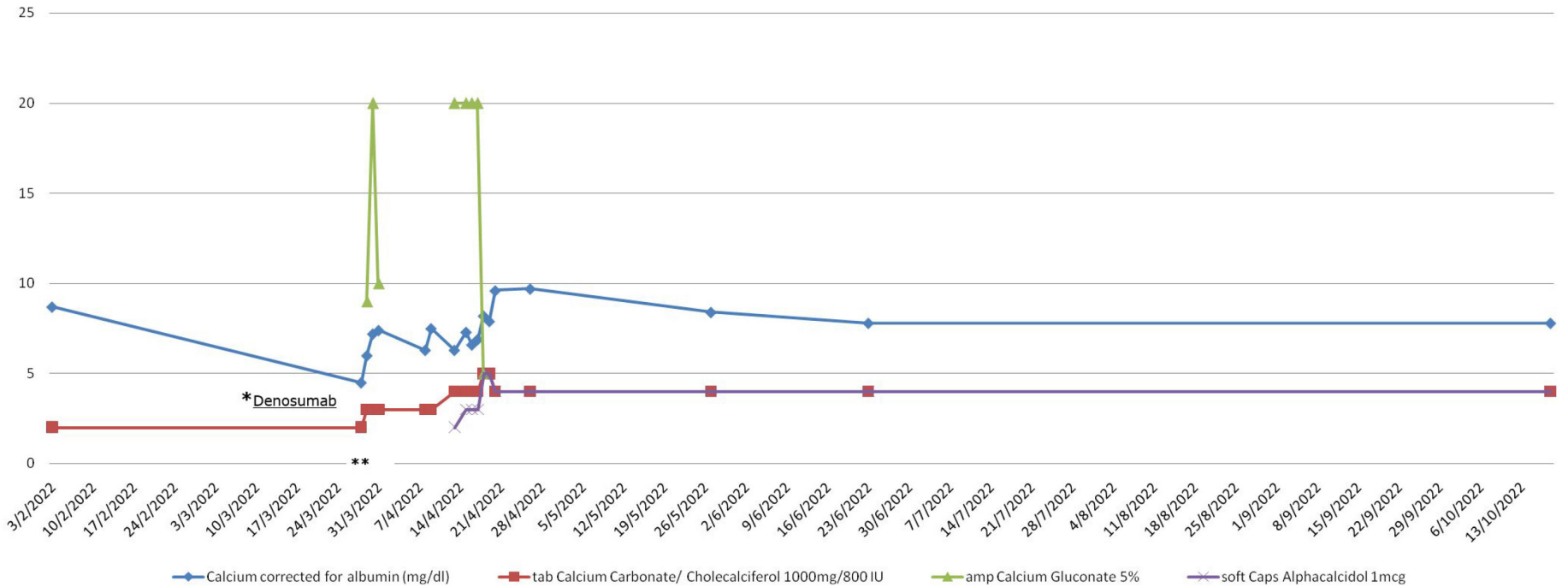

Figure 1. The left axis represents absolute numbers for serum Calcium corrected for albumin (measured in mg/dl), tablets of administered Calcium Carbonate/Cholecalciferol (1000 mg/800 IU), ampoules of administered Calcium Gluconate 5%, and soft capsules of administered Alphacalcidol (1 mcg). *Denosumab was administered on 10/03/2022, **admission to the hospital.

calcium gluconate 5% and started a weekly 25.000 IU cholecalciferol regimen. Her corrected for albumin calcium, although never normalized, remained steady at 7.4-7.5 mg/dl the last 48 hours of her hospitalization even with the withdrawal of intravenous calcium infusion. Due to the fact that the patient was asymptomatic, she was discharged on oral calcium carbonate/cholecalciferol 1000 mg/800 IU three times daily.

The patient returned six days later for the scheduled lab checkup and the work-up revealed a corrected calcium level of 6.3 mg/dl (she was asymptomatic), therefore she was admitted again to the hospital. A more intensive regimen took place during her second-time hospitalization, including 4 g of calcium carbonate, 3200 IU cholecalciferol and 2 mcg of alfacalcidol per day, added to 20g of calcium gluconate iv daily. This regimen was maintained for 4 days and then our team attempted to discontinue the iv infusion, so the *per os* doses were increased to 5g of calcium carbonate, 4000 IU cholecalciferol and 5mcg alfacalcidol daily. On the 11th day of hospitalization, the level of corrected calcium was 7.9 mg/dl, which was considered as acceptable for discharge. She was advised to receive a dose of 4 g of calcium carbonate combined with 3200 IU of cholecalciferol, and 4mcg of alfacalcidol daily. A remarkable point was that despite the intensive intravenous and *per os* administration of calcium, hypercalciuria was not present (Ca: 41 mg/24h, normal range NR: 100-300 mg/24h, Cr: 4, 3 mg/24h NR: 500- 2000 mg/24h).

Outcome and follow-up

One month later, at the scheduled follow-up appointment, the laboratory results revealed a corrected for albumin calcium level of 8.4 mg/dl. An interesting fact

that our team observed was that the following month (two months after her hospitalization) the calcium level dropped again to a level of 7.8 mg/dl (corrected for albumin). She was asymptomatic and therefore she was not hospitalized. During her monthly check-ups, calcium levels were mostly at the range of 7.5 mg/dl to 7.7 mg/dl, therefore a gradual modification of her *per os* regimen has been attempted, to a dose of calcium carbonate 1000 mg, 800 IU cholecalciferol and 0.5mg of alfacalcidol daily (Figure 1, Table 2).

Discussion

Denosumab, a RANK-L ligand inhibitor, appears to be an effective anti-osteoporotic treatment and unlike bisphosphonates, it is not excreted by the kidney. However, little is known about its safety and efficacy in patients with chronic kidney disease. We searched PubMed for reviews and case-reports regarding patients with CKD and hypocalcemia after treatment with denosumab. There is a very limited number of studies, so we cannot extract a reliable conclusion. In this context, we realized that it will be really interesting if we present this challenging to treat hypocalcemia after the third denosumab injection in a patient with an autoimmune disorder background and simultaneously impaired renal function.

The results from previous studies and case reports (albeit small in number) were contradictory. Jamal et al. concluded that denosumab was not associated with increased cases of adverse effects in patients with impaired renal function[9], however two case reports supported the fact that hypocalcemia in patients with chronic renal disease can be severe and more refractory to treatment comparing to patients with normal eGFR, even mimicking hungry bone syndrome[10,11]. The reason why patients with chronic kidney disease are at a higher risk for hypocalcemia following denosumab therapy is not well understood though. Block et al. suggested that it is possibly attributed to the pharmacodynamic effect, because pharmacokinetic studies on denosumab do not show significant difference among concentration-time profiles based on the kidney function[12]. Several numbers of studies have suggested an association between renal dysfunction and increased risk of hypocalcemia post-denosumab[13,14]. Moreover, studies show that given the fact that there is no negative impact of denosumab administration on renal function and the drug is not excreted or metabolized by the kidneys there is practically no need for dose adjustment during therapy with the aforementioned drug[12]. In addition, in FREEDOM trial substantial attention was given to the fact that long-term denosumab treatment was not associated with a decline in renal function[8], confirming results from previous studies with 3-year denosumab administration in patients with CKD[9].

An interesting finding in the study of Imatoh et al. is the connection between elevated serum ALP levels before initial prescription of denosumab and subsequent hypocalcemia[15]. This relationship was observed also by Kinosita et al.[16]. In adults with a normal liver function, approximately fifty per cent of the total serum ALP is derived from bone[17]. Alkaline phosphatase is a marker of osteoblastic differentiation and subsequently marker of bone formation. As we mentioned in the introduction, osteoblasts express RANK-L on the extracellular surface of the osteoclasts. This results to possible hypocalcemia induction by denosumab, via excess RANK-L inhibition. Hence, an elevated level of ALP in the serum can be a predictor for hypocalcemia following therapy with denosumab[15], which was not the case in our patient, as ALP values were always within the normal range. The number of studies concerning this parameter is limited though. As a final point, we can add that multivariate logistic regression analysis in the study by Okada et al.[14], revealed that the patients who were not treated with zoledronic acid before administration of denosumab as a therapy for osteoporosis, had a higher risk of hypocalcemia induced by denosumab. The same study showed that creatinine clearance less than 50 ml/min was an independent risk factor for hypocalcemia after denosumab.

Therefore, a safe conclusion cannot be extracted, as renal failure is without doubt a known risk factor for hypocalcemia and renal impairment per se can increase the risk of hypocalcemia regardless of administration of denosumab.

Conclusion

An interesting case of severe and refractory to treatment hypocalcemia in a patient with a background of systemic lupus erythematosus, and lupus nephritis, provided our department with the opportunity to investigate further and review similar cases. However, the data is limited, as there is not a vast number of studies in order to confirm that there is a higher risk in patients with renal failure to develop severe and life-threatening hypocalcemia after denosumab therapy. In addition, more studies are needed to extract a safe conclusion about the risk factors for hypocalcemia in this group of patients. We all agree though, that if denosumab is used in patients with chronic renal disease, close monitoring and more aggressive regimen regarding replacement of calcium is required in order to avoid severe hypocalcemia that may lead to hospitalization and further complications.

References

1. Ensrud KE, Lui L-Y, Taylor BC, et al. Renal function and risk of hip and vertebral fractures in older women. Arch Intern Med 2007;167:133–139.
2. Chen H, Lips P, Vervloet MG, et al. Association of renal function with bone mineral density and fracture risk in the longitudinal aging study Amsterdam. Osteoporos Int 2018;29:2129–2138.
3. Mittalhenkle A, Gillen DL, Stehman-Breen CO. Increased risk of mortality associated with hip fracture in the dialysis population. Am J Kidney Dis 2004;44:672–679.

4. Coco M, Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. Am J Kidney Dis 2000;36:1115–1121.
5. Fizazi K, Bosserman L, Gao G, Skacel T, Markus R. Denosumab treatment of prostate cancer with bone metastases and increased urine N-telopeptide levels after therapy with intravenous bisphosphonates: results of a randomized phase II trial. J Urol 2013;189(1 Suppl):S51-S58.
6. AMGEN. Denosumab product monograph. https: www.amgen.ca. Accessed 24 April 2020.
7. Langdahl BL, Teglbjærg CS, Ho PR, et al. A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: results from the ADAMO trial. J Clin Endocrinol Metab 2015;100(4):1335-1342.
8. Broadwell A, Chines A, Ebeling PR, et al. Denosumab Safety and Efficacy Among Participants in the FREEDOM Extension Study with Mild to Moderate Chronic Kidney Disease. J Clin Endocrinol Metab 2021;106(2):397-409.
9. Jamal SA, Ljunggren Ö, Stehman-Breen C, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. J Bone Miner Res 2011; 26:1829-1835.
10. Nachankar A, Katyal A, Bansal N, Bishnoi A. Hungry bone syndrome like presentation following single-dose denosumab for hypercalcaemia secondary to sarcoidosis with IgA nephropathy. BMJ Case Rep 2022; 15(7): e250647.
11. Dave V, Chiang CY, Booth J, Mount PF. Hypocalcemia post denosumab in patients with chronic kidney disease stage 4-5. Am J Nephrol 2015;41(2):129-37.
12. Block GA, Bone HG, Fang L, Lee E, Padhi D. A single-dose study of denosumab in patients with various degrees of renal impairment. J Bone Miner Res 2012; Jul; 27(7):1471-9.
13. Huynh ALH, Baker ST, Stewardson AJ, et al. Denosumab-associated hypocalacemia: incidence, severity and patient characteristics in a tertiary hospital setting. Pharmacoepidemiol Drug Saf 2016;25:1274-1278.
14. Okada N, Kawazoe K, Teraoka K, et al. Identification of the risk factors associated with hypocalcemia induced by denosumab. Biol Pharm Bull 2013;36:1622-1626.
15. Imatoh T, Sai K, Takeyama M, Hori K, Karayama M, Furuhashi K, Segawa K, Kimura M, Kawakami J, Saito Y. Identification of risk factors and development of detection algorithm for denosumab-induced hypocalcaemia. J Clin Pharm Thera 2019;44(1):62-68.
16. Kinoshita Y, Arai M, Ito N, et al. High serum ALP level is associated with increased risk of denosumab-related hypocalcemia in patients with bone metastases from solid tumors. Endocr J 2016;63:479-484.
17. Delmas PD, Eastell R, Garnero P, et al. The use of biochemical markers of bone turnover in osteoporosis. Committee of Scientific Advisors of the International Osteoporosis Foundation. Osteoporos Int 2000; 11(Suppl 6): S2-S17.