中文題目：保骼麗 Denosumab 引起嚴重低血鈣症：病例報告
英文題目：Denosumab induced severe hypocalcemia: A case report
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Introduction:
The biologic agent denosumab, also marketed as Prolia®, a monoclonal antibody that inhibits RANK ligand, reduces the number of active osteoclasts, reduces bone resorption, and increases bone mass, is an approved agent for the treatment of osteoporosis. The occurrence of severe hypocalcemia after denosumab injection was uncommon but might be life-threatening. Fatal cases have been reported with concomitant renal impairment. We report a case of denosumab-induced severe hypocalcemia following a single denosumab injection.

Case Report:
The patient is an 88-year-old woman with the past medical history of hypertension, type 2 diabetes, stage 4 chronic kidney disease (CKD), and osteoporosis. She received a dose of denosumab for the treatment of osteoporosis and tolerated well after injection. Fifty days later, she presented with progressive and severe weakness that prevented her from getting out of bed, accompanied by psychomotor slowing and drowsiness. It was also associated with poor appetite with malnourished in recent 1 month. She denied seizures, syncope, chest pain, or palpitations. Neurological examination revealed 2/5 strength in all extremities. The Chvostek sign was absent.

Blood examination revealed a serum total calcium of 4.5 mg/dL (normal 8.6–10 mg/dL), magnesium 1.82 mg/dL (normal 1.8–2.5 mg/dL), phosphorus 1.8 mg/dL (normal 2.4–4.7 mg/dL), 25-hydroxy vitamin D 2.9 ng/mL (normal 30–100 ng/mL), alkaline P 42 IU/L (normal 32-91 IU/L) and intact PTH was 3145 pg/mL (normal 15–68 pg/mL). Her eGFR on admission was 24 mL/min/1.72m2, and her serum creatinine was 2 mg/dL (baseline between 1.9 and 2.3 mg/dL). Eleven months before admission she had serum calcium of 8.9mg/dL. ECG revealed a prolonged QT interval of >500 ms. The patient received intravenous 400 mg of calcium chloride infusion every 8 hours for 1 week, which significantly improved her serum calcium levels from 4.5 to 8.1 mg/dL, resolved the weakness and normalized QTc interval. The patient received oral supplementation with calcitriol 0.25 mcg twice per day after being discharged.

Discussion:
We reported a case report of severe hypocalcemia following a denosumab injection. Several risk factors precipitated this event including old age, chronic kidney disease, and vitamin D deficiency. Denosumab is generally preferred over zoledronic acid in patients with chronic kidney disease because it is not cleared by the kidney and is technically not nephrotoxic. A paucity of data regarding the safety of denosumab use in patients with advanced renal disease. Severe hypocalcemia (i.e., <7 mg/dL) or symptomatic hypocalcemia was seen in the late stages of renal disease. In one observational study, 45 percent of the patients with baseline eGFR < 30 ml/min developed hypocalcemia during treatment with denosumab. A dose-reduction strategy in CKD has been evaluated in only one case series study by Cicci et al. of refractory hypercalcemia due to multiple myeloma and acute kidney injury. They proposed the novel dosing strategy of 0.3 mg/kg of denosumab based on 4 case reports in patients with multiple myeloma over a fixed,

reduced dose of 60 mg (from the standard 120 mg) in patients with renal dysfunction. Despite dose reduction, three out of four patients developed mild hypocalcemia with the effect lasting for 15–40 days. Similarly, our patient developed severe hypocalcemia although she was received 60mg of Denosumab. It requires further validation in large-scale studies.

There have been few cases reported of denosumab-induced hypocalcemia in the context of vitamin D deficiency and chronic kidney disease. One retrospective study evaluated patients with chronic kidney disease stage 4–5 showed the time to the lowest corrected calcium after injection varied between 10 and 71 days with a median period of 21 days. Initial monitoring of calcium, ideally 8-14 days post-administration should be done with all patients at risk of hypocalcemia. Delayed presentation with hypocalcemia can also occur such as in this case where the patient presented 50 days post-injection.

Hypophosphatemia has been shown to occur in 2.1% of patients treated with denosumab. In our patient, her serum phosphorus was 1.8 mg/dL, no doubt exacerbating her weakness on admission. Her intact PTH was 3145 pg/mL, presumably enough to cause phosphaturia. In addition, her vitamin D deficiency, likely due to malnutrition and other possible cause such as chronic bedridden, contributed to the hypocalcemia and hypophosphatemia. Prospective studies are needed to explore the safety profile of denosumab.

Conclusion:
This case highlights the importance of screening and ongoing monitoring of risk factors for iatrogenic hypocalcemia. Denosumab should be avoided or used with caution in advanced chronic kidney disease due to the potentially life-threatening, severe hypocalcemia that has been observed. Further research is needed to determine the clinical utility of bone turnover markers; however, they may be helpful tools to physicians to help determine a patient’s risk of hypocalcemia before starting denosumab.