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From the Clinic

Dramatic increase in parathyroid hormone and hypocalcaemia after denosumab in a kidney transplanted patient

de Beus *et al*. report a case of a patient with immobilization-related hypercalcaemia and advanced renal insufficiency that did not respond to bisphosphonates, and after a single dose of denosumab (60 mg), a rapid and sustained decrease of the serum calcium concentration was observed with a transient hypocalcaemia which needed the introduction of oral calcium and active vitamin D to correct it [1]. Simultaneously with hypocalcaemia, the patient showed a moderate increase in parathyroid hormone (PTH) levels in blood.

As discussed in an editorial by Malberti in the same issue [2], denosumab is a fully humanized monoclonal antibody that is a promising therapeutic option for osteoporosis [2, 3]. It has demonstrated efficacy and safety among individuals with chronic kidney disease [4], but an increased frequency of moderate hypocalcaemia has been reported in those with decreased kidney function and those on haemodialysis [5, 6], so this negative effect can be useful in the treatment of hypercalcaemia as in the case described. Unfortunately, the different published studies do not evaluate the evolution of PTH.

We report a case of dramatic increase of PTH levels in blood with persistent hypocalcaemia 6 months after a 60 mg dose of denosumab. Our patient is a 64-year-old woman with a functioning renal allograft for 18 years. At present, the patient has a chronic rejection confirmed by a biopsy and stable renal function during the last 10 years (Modification of Diet in Renal Disease between 25–30 mL/min).

The treatment includes tacrolimus 2 mg every 12 h, prednisone 5 mg/day and Hidroferol® (Calcifediol) 16.000 IU every 2 weeks, The patient is routinely visited at our outpatients' area every 6 months, she had a recent history of bone pain, a spontaneous fracture and osteoporosis so a single subcutaneous 60 mg dose of denosumab was prescribed.

Before denosumab administration, she showed normal serum values of calcium, phosphorus, alkaline phosphatases and 25 vitamin D. Intact PTH (iPTH) was slightly elevated (442 pg/mL).

After denosumab administration, the patient showed no secondary effects. When the patient was followed up at 6 months, the laboratory test showed a decrease in the total corrected calcium level in blood from 2.44 mmol/L (9.8 mg/dL) to 1.91 mmol/L (7.7 mg/dL) and a dramatic increase in the iPTH blood level from 442 pg/mL to 1.745 pg/mL. The serum alkaline phosphatase level decreased from 238 U/L to 105 U/L and other blood parameters (renal function, phosphorus, C-reactive protein, ferritin, 25 vitamin D and tacrolimus) and calcium excretion remained stable. At 6 months, the scheduled dose of denosumab was cancelled.

The observed dramatic increase in PTH level in our patient was unexpected and has no obvious explanation. It cannot be explained exclusively by hypocalcaemia and may well be due to other unknown mechanisms. We also do not yet know the effects of sustained high PTH levels in the blood in this case.

Our message is that at present we should be very cautious using denosumab in patients with renal dysfunction, and in cases where it is used, strict control of calcium and PTH levels in the blood is vital.

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Editorial Note: Dr de Beus *et al*. had no further comments on this letter.

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