5. Recurrent hypocalcemia following denosumab in a patient with short bowel and renal impairment.

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Background: Because of the high osteoporosis prevalence in patients requiring HPTN, a comprehensive protocol for BMD maintenance and improvement was instituted, including oral calcium, vitamin D ± calcitriol, parenteral bisphosphonates and newer agents.

Case report: A 69-year-old woman with Crohn's disease began HPTN 14 years ago with serum creatinine of 140 μmol/L. Unchanged for 11 years, it rose to 160 over two years, then more rapidly. TPN volume was 1.3-2 L/day; urine output remained 1.5 L/day. Past osteoporosis treatments included HRT (15 Yr), calcitonin, IV bisphosphonates, raloxifene, and vitamin D, alfacalcidol, calcitriol 0.25 μg/day and $CaC0_3$ 1.5 g/day. BMD T-scores were stable the last 4 years (hip -2.2, spine -2.6).
She received denosumab 60 mg on January 31, 2014; prior total Ca 2.37 mmol/L, ionized Ca 1.22 mmol/L, 25 (OH)D 47pmol/L, PTH 19.8 pmol/L, creatinine 528 μmol/L. At the ER 3 weeks later for symptomatic hypocalcemia, total Ca was 1.43 mmol/L, ionized Ca 0.76 mmol/L, PTH 83.4 pmol/L, creatinine 458 μmol/L. After 3 days treatment with IV NS and Ca gluconate, calcitriol 0.25 μg tid and $CaCO_3$ 4 g/day, total Ca was 2.20 mmol/L, ionized Ca 1.17 mmol/L and creatinine 443 μmol/L.
Over the next 3 weeks, calcium tended downward to 1.73 mmol/L, but by the end of 5 weeks, was 2.70 mmol/L. Calcitriol was decreased to 0.25 μg/day and $CaCO_3$ to 1.5 g/day. Total calcium increased to 2.98 mmol/L by 6 weeks, so both were stopped. An unexplained 3-day bout of increased ileostomy output occurred and 5 days later, she had severe generalized muscle spasms. Total Ca was 1.73mmol/L, ionized Ca 1.00 mmol/L, Mg 0.56 mmol/L and creatinine 611 mmol/L. Again, IV NS and boluses of Ca gluconate and also $MgSO_4$ were given. Calcitriol and $CaCO_3$ were restarted at the last doses. Two days later, total Ca was 1.97 mmol/L, ionized Ca 1.13 mmol/L, and creatinine 466 μmol/L. At 11 weeks post denosumab, they were 2.03 mmol/L, 1.10 mmol/L and 428 μmol/L, respectively.

Discussion: This case demonstrates that although denosumab is indicated in renal insufficiency, when severe, there is a prolonged risk of recurrent hypocalcemia. This indication was not based on adequate data for advanced renal failure. Though Ca 1g/day and vitamin D 400 IU/day and "clinical monitoring of calcium levels" are recommended, use of calcitriol is not included. Use in dialyzed patients (± secondary hyperparathyroidism) has demonstrated that hypocalcemia needs aggressive monitoring, calcitriol and high-dose calcium. With diarrhea, the severity of hypocalcemic manifestations may be exacerbated by hypomagnesemia, mandating Mg monitoring. Intensive management of bone status in HPTN patients can maintain BMD.