EXCEPTIONAL CASE

Severe hypercalcaemia early after kidney transplantation in two patients with severe secondary hyperparathyroidism previously treated with etelcalcetide

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ABSTRACT

Cinacalcet and, more recently, etelcalcetide revolutionized the treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). Kidney transplant (KT) usually improves CKD–MBD. However, a significant proportion of KT recipients have high serum calcium levels, not requiring any treatment. We report two patients previously treated with etelcalcetide who developed severe (>3.3 mmol/L) hypercalcaemia in the early post-KT course, requiring parathyroidectomy. Pathological studies showed parathyroid adenomas and hyperplasia. One patient had a graft biopsy showing numerous intratubular calcium phosphate crystals. These observations should prompt pharmacovigilance studies and careful follow-up of KT recipients previously treated with etelcalcetide.

Keywords: calcimimetics, etelcalcetide, haemodialysis, hypercalcaemia, kidney transplant, parathyroidectomy

BACKGROUND

Secondary hyperparathyroidism (SHPT) is a common long-term complication of chronic kidney disease (CKD) affecting most patients on maintenance haemodialysis. SHPT treatment has been revolutionized by the successive availability of cinacalcet and etelcalcetide [1, 2]. The latter, an intravenously administered direct calcium-sensing receptor agonist, became available in 2017 for the treatment of SHPT in adults undergoing haemodialysis, and is now widely used worldwide [3]. In contrast to cinacalcet, the potential post-kidney transplant (KT) consequences of etelcalcetide use in KT candidates have not been reported yet. We report severe hypercalcaemia early after KT in two patients treated with etelcalcetide while on haemodialysis.
CASE REPORTS

Patient 1, a 62-year-old Caucasian male, received a deceased-donor KT for end-stage kidney disease (ESKD) secondary to vascular nephropathy. After 3 years of CKD stage 5 and untreated SHPT, haemodialysis was started, 9 months before KT. He was given 15 mg etelcalcetide (as first calcimimetic treatment) per haemodialysis session for the last 8 months. His treatment also included cholecalciferol 25 000 UI every 2 weeks. Dialysate calcium concentration was 1.5 mmol/L. On the day of transplantation, intact parathyroid hormone (iPTH) level was at 463 pg/mL (normal range = 15–80 pg/mL, Cobas e602 module, Roche). The last injection of etelcalcetide was performed the day before transplantation. Post-KT regimen included mycophenolate mofetil, tacrolimus, methylprednisolone, valganciclovir and cotrimoxazole prophylaxis, simvastatin, low-dose acetylsalicylic acid, sodium bicarbonate, allopurinol and pantoprazole. On Day 2, the patient developed hypercalcaemia that rapidly worsened (Figure 1). Although he remained asymptomatic, subtotal parathyroidectomy (PTX) was performed on Day 16 because of uncontrolled hypercalcaemia peaking at 3.46 mmol/L (normal range = 2.2–2.55 mmol/L). Phosphataemia was 0.85 mmol/L. Three days before PTX, calciuria and phosphaturia reported to urine creatinine (mg/dL:mg/dL) were 0.34 and 0.82, respectively. Histology of parathyroids revealed four adenomas and parathyroid hyperplasia. After PTX, graft function worsened. A graft biopsy was performed on Day 21 post-KT and showed multiple intratubular calcium phosphate crystals in the medulla, with no sign of acute rejection. Three months after KT, allograft function remained impaired with an estimated glomerular filtration rate (eGFR) of 36 mL/min/1.73 m².

Patient 2 is a 35-year-old Caucasian female who received a deceased-donor KT for ESKD of unknown aetiology. She was transplanted after 8 years of haemodialysis. SHPT developed and was first treated with cinacalcet 60 mg/day for 1 year (initially with a good control of iPTH but eventually interrupted for digestive intolerance), and then by etelcalcetide 5 mg thrice weekly for the last 19 months (last dose given the day before KT). She also received alfalcacidol from July 2018 until KT in September 2020. Dialysate calcium concentration was 1.5 mmol/L. iPTH level was at 638 pg/mL before transplantation. The immediate post-transplant course was complicated by delayed graft function, requiring haemodialysis (Figure 1). The patient’s regimen included mycophenolate mofetil, tacrolimus, methylprednisolone, valganciclovir and cotrimoxazole prophylaxis, amiodipine, low-dose acetylsalicylic acid and pantoprazole. She developed hypercalcaemia on Day 13 and underwent subtotal PTX on Day 34 because of uncontrolled, poorly tolerated (recurrent vomiting) hypercalcaemia of up to 3.42 mmol/L. Phosphataemia was 1.36 mmol/L. Three days before KT, calciuria and phosphaturia reported to urine creatinine (mg/dL:mg/dL) were 0.053 and 0.59, respectively. Histology of parathyroids revealed three adenomas and parathyroid hyperplasia. Three months after KT, allograft function remained impaired (eGFR 35 mL/min/1.73 m²).

Immediate evolution after PTX was uncomplicated in both patients. Neither experienced either hungry bone syndrome or hypocalcaemia. Only a slight, transient, elevation of the alkaline phosphatase level was observed in Patient 1 (<130% of the upper normal value). Two weeks after PTX, calciuria and phosphaturia reported to urine creatinine (mg/dL:mg/dL) were 0.08 and 0.75 in Patient 1, and 0.035 and 0.44 in Patient 2, respectively. iPTH level was at 126 pg/mL in Patient 1 and at 116 pg/mL for Patient 2, 3 months after PTX. The patients have not developed hypoparathyroidism so far.

DISCUSSION

We report for the first time two cases of severe hypercalcaemia developing early after KT in patients previously treated with etelcalcetide. These two patients are the very first to have been transplanted in our kidney centre after receiving this drug during dialysis.

KT corrects, at least partly, CKD–MBD in most KT recipients [4]. Nevertheless, ~25% of patients keep elevated iPTH levels after transplantation. This hyperparathyroidism originates either from persistent CKD–MBD characterized by, among others, previous parathyroid hyperplasia associated with an elevated calcium set-point for inhibition of PTH secretion, or from the improved ‘skeletal resistance’, an often unnoticed condition of hyporesponsiveness to PTH effect, resulting from multiple factors, including uremia per se [5]. Mild hypercalcaemia secondary to persistent hyperparathyroidism is observed in around 30% of KT recipients at 1 year [6], whether they have been previously treated by cinacalcet or not. Prior cinacalcet treatment has been shown to potentially be associated with secondary hyperparathyroidism rebound, nephrocalcinosis and hypercalcaemia developing usually months after KT [6]. Hypercalcaemia usually does not exceed 2.9 mmol/L and rarely requires any acute treatment, i.e. PTX or cinacalcet re-introduction [7], the latter has even been reported as effective in the treatment of post-KT nephrocalcinosis [8]. In contrast, the hypercalcaemia observed in our two patients developed very early after KT, was severe and required urgent PTX.

FIGURE 1: Biological evolution after kidney transplantation. Plasma creatinine, calcium and phosphate levels are represented. Blue arrows point to the kidney transplant date (Day 0) and green arrows to subtotal parathyroidectomy. Patient 2 underwent haemodialysis until Day 12. Left y-axis indicates total serum calcium and phosphate levels (mmol/L) and right y-axis indicates serum creatinine levels (mg/dL).
Cinacalcet and etelcalcetide have several differences. First, compared with cinacalcet, etelcalcetide is associated with greater reductions in iPTH, serum calcium and fibroblast growth factor-23 concentrations in dialysis patients with hyperparathyroidism [1]. Secondly, the dropout rate of cinacalcet treatment is high, and contrasts with etelcalcetide, which is usually better tolerated than cinacalcet, and whose adherence is almost ‘guaranteed’ by the intravenous administration of the drug at each haemodialysis session [3, 9]. For these reasons, dialysis patients treated with etelcalcetide at the time of transplantation might have a more severe hyperparathyroidism disease than those treated by cinacalcet. The abrupt withdrawal of etelcalcetide after KT, potentiated by its fast elimination by the normalized kidney function [10], may thus induce rebound autonomous hyperparathyroidism. This would trigger rapid post-transplant hypercalcaemia development, potentially through the response of the kidney allograft to the hyperactivated PTH–calcitriol axis as well as through its participation in the PTH-independent calcium control mechanisms.

Larger studies are required to confirm our observation and assess the causal relationship between etelcalcetide and severe post-KT hypercalcaemia. However, we have never observed such a severe clinical presentation while we have routinely managed KT recipients previously treated with cinacalcet for the last 15 years. These observations should prompt pharmacovigilance studies and careful post-KT follow-up of haemodialysis patients previously treated with etelcalcetide.

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AUTHORS’ CONTRIBUTIONS
G.D. and A.D. contributed to data acquisition, data analysis and writing of the manuscript; G.D., J.-M.P., L.L., A.B., V.G., M.J., N.K. and A.D. took care of the patients. All authors discussed and reviewed the article.

CONFLICT OF INTEREST STATEMENT
The results presented in this article have not been published previously. L.L. reports lecture fees and travel grant from Amgen, outside the submitted work. M.J. reports research grants from Amgen, outside the submitted work; other: cochair of Kidney Disease: Improving Global Outcomes (KDIGO) since 2019. J.-M.P. reports lecture fees and consultant fees for Amgen, outside the submitted work. G.D., A.B., V.G., N.K. and A.D. declare to have no relevant financial interests.

PATIENT CONSENT
The patients gave informed consent to publish their case.

REFERENCES
1. Eidman KE, Wetmore JB. Treatment of secondary hyperparathyroidism: how do cinacalcet and etelcalcetide differ? Semin Dial 2018; 31: 440–444
2. Block GA, Bushinsky DA, Cunningham J et al. Effect of etelcalcetide vs placebo on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism: two randomized clinical trials. JAMA 2017; 317: 146–155
3. Russo D, Tripepi R, Malberti F et al. Etelcalcetide in patients on hemodialysis with severe secondary hyperparathyroidism. Multicenter study in “real life”. J Clin Med 2019; 8: 1066
4. Evenepoel P, Claes K, Kuypers DR et al. Parathyroidectomy after successful kidney transplantation: a single centre study. Nephrol Dial Transplant 2007; 22: 1730–1737
5. Bover JU-T, Evenepoel P, Lloret MJ et al. PTH receptors and skeletal resistance to PTH action. In: Covic A, Goldsmith D, Urena Torres PA (eds). Parathyroid Glands in Chronic Kidney Disease. Cham: Springer, 2020, 51–77
6. Evenepoel P, Sprangers B, Lerut E et al. Mineral metabolism in renal transplant recipients discontinuing cinacalcet at the time of transplantation: a prospective observational study. Clin Transplant 2012; 26: 393–402
7. Cruzado JM, Moreno P, Torregrosa JV et al. A randomized study comparing parathyroidectomy with cinacalcet for treating hypercalcemia in kidney allograft recipients with hyperparathyroidism. J Am Soc Nephrol 2016; 27: 2487–2494
8. Cheunsuchon B, Sritippayawan S. Successful treatment of early allograft dysfunction with cinacalcet in a patient with nephrocalcinosis caused by severe hyperparathyroidism: a case report. BMC Res Notes 2017; 10: 153
9. Fuller DS, Hallett D, Dluzniewski PJ et al. Predictors of cinacalcet discontinuation and reinitiation in hemodialysis patients: results from 7 European countries. BMC Nephrol 2019; 20: 169
10. Subramanian R, Zhu X, Kerr SJ et al. Nonclinical pharmacokinetics, disposition, and drug-drug interaction potential of a novel d-amino acid peptide agonist of the calcium-sensing receptor AMG 416 (etelcalcetide). Drug Metab Dispos 2016; 44: 1319–1331