Combination Therapy of Denosumab and Calcitriol for a Renal Transplant Recipient with Severe Bone Loss due to Therapy-Resistant Hyperparathyroidism

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Denosumab (DMAb), a complete human type monoclonal antibody directed against the receptor activator of nuclear factor-κB ligand, has gained attention as a novel treatment for osteoporosis. However, its efficacy in patients with chronic kidney disease (CKD) remains unclear. We describe a 64-year-old man with severe bone loss and persistent secondary hyperparathyroidism (SHPT) after renal transplantation, whose condition failed to respond to conventional pharmacologic or surgical interventions. He underwent parathyroidectomy with left forearm autograft of crushed tiny parathyroid gland (PTG) particles. However, the autografted PTGs became swollen and caused persistent SHPT in spite of two additional parathyroidectomies of the left forearm. A single subcutaneous administration of DMAb induced hypocalcemia, which was corrected by calcium supplementation and high-dose calcitriol. Eventually, combination therapy with DMAb and calcitriol led to a decline in the patient’s elevated serum parathyroid hormone levels, normalization of laboratory markers of bone metabolism, and improvement in bone mineral density in a short period of time. To the best of our knowledge, this is the first case report of severe bone loss with persistent SHPT in a renal transplant recipient effectively treated with the combination therapy of DMAb and vitamin D (VD). Although DMAb itself exerts no direct effects on PTGs, the DMAb treatment improved the patient’s bone loss. In addition, administration of DMAb allowed for high-dose VD therapy which ultimately controlled SHPT and prevented DMAb-induced hypocalcemia. Therefore, this combination therapy might be a reasonable therapeutic strategy to reverse severe bone loss due to therapy-resistant SHPT in patients with CKD.

Keywords: bone loss; denosumab; hypocalcemia; secondary hyperparathyroidism; vitamin D

Introduction

Renal transplantation (RT) is effective in correcting the main causal factors of secondary hyperparathyroidism (SHPT) including uremia, phosphate retention, and vitamin D (VD) deficiency (Messa et al. 1998). Nevertheless, persistent SHPT characterized by hypercalcemia, hypophosphatemia, and elevated parathyroid hormone (PTH) in renal transplant recipients is quite common, even after successful RT (Messa et al. 1998; Douthat et al. 2012). According to previous reports, approximately 50% of renal transplant recipients continue to have SHPT at one year after RT (Douthat et al. 2012). According to previous reports, approximately 50% of renal transplant recipients continue to have SHPT at one year after RT (Douthat et al. 2012; Cohen et al. 2012), and 20% of recipients retain high levels of PTH at 5 years after RT (Bertoni et al. 2006). Persistent SHPT is known to cause bone loss, bone pain, and fracture. Moreover, it has been demonstrated that persistent SHPT is associated with poor graft function and adverse cardiovascular outcomes (Egbuna et al. 2007; Covic et al. 2009; Evenepoel et al. 2014). Therefore, adequate management of persistent SHPT after RT is a critical issue.

Denosumab (DMAb) is a complete human type monoclonal antibody directed against the receptor activator of nuclear factor-κB ligand (RANKL) (Ivashkiv et al. 2011). By its action on RANKL, DMAb reduces the signal that is essential for formation, maturation, function and survival of osteoclasts (Ivashkiv et al. 2011). Administration of DMAb has shown strong inhibitory effects on bone resorption (Cummings et al. 2009) and thereby, like bisphosphonates, is currently utilized for treatment of osteoporosis in postmenopausal women and in men at increased risk for fractures (Cummings et al. 2009; Silverman and Christiansen 2012; Nakamura et al. 2014). In addition, subcutaneous administration of DMAb every 6 months is sufficient to
obtain inhibitory effects on bone resorption because of its long half-life in the body (Cummings et al. 2009; Ivashkiv et al. 2011). Since DMAb is not cleared by the kidneys, no dosage adjustment according to renal function is required (Block et al. 2012). Therefore, we consider that this agent is beneficial for chronic kidney disease (CKD) patients with bone loss, especially for whom bisphosphonates are not recommended because of severe renal dysfunction (defined as estimated glomerular filtration rate (eGFR) < 30 mL/min). In particular, DMAb is highly expected to be efficacious in CKD patients complicated with mineral and bone disease (MBD), including not only bone loss but also SHPT. However, until now, there has been no sufficient evidence to support the efficacy of DMAb in treating MBD in this population. Moreover, previously reported cases have indicated that caution is needed in the administration of DMAb because it induced severe hypocalcemia in patients with CKD (Talreja 2012; McCormick et al. 2012; Torregrosa 2013; Agarwal et al. 2013; Ungprasert et al. 2013; Farinola and Kanjanapan 2013; Dusilova Sulkova et al. 2014).

We describe a 64-year-old man with severe bone loss and persistent SHPT after RT, whose condition failed to respond to conventional pharmacologic or surgical interventions. Combination therapy with DMAb and a high dose of an active VD achieved improvement in the patient’s bone loss and SHPT. As far as we know, this is the first case report of severe bone loss due to therapy-resistant SHPT in a renal transplant recipient effectively treated with this combination therapy. Herein, we discuss the efficacy and safety of this combination therapy in patients with CKD.

**Case Presentation**

Our patient began hemodialysis (HD) for end-stage renal disease (ESRD) due to unknown cause in 1973, when he was 23 years old. In 1994, he developed severe SHPT that was unresponsive to dietary restrictions, phosphate binders, and VD therapy. He underwent parathyroidectomy with left forearm autograft of crushed tiny parathyroid gland (PTG) particles. However, severe SHPT recurred in two years, and he received percutaneous ethanol injection therapy (PEIT) to the enlarged PTGs in his left forearm, where resected parathyroid tissue had been autografted. Unfortunately, the PTH value remained high despite frequent PEIT. The bone mineral density (BMD) of the femoral neck and distal radius on the non-shunt side by dual-energy X-ray absorptiometry (DEXA, QDR-Discovery; Hologic, Inc., Waltham, MA, USA) showed low levels (0.679 and 0.481 g/cm², respectively).

In November 2006, he underwent ABO-incompatible RT from his 54-year-old wife. His primary immunosuppressive regimen was composed of cyclosporine (CyA), mycophenolate mofetil (MMF), and methylprednisolone (mPSL). The postoperative course was satisfactory with one episode of mild antibody-mediated rejection, which was treated successfully with mPSL pulse therapy. However, the patient’s SHPT did not improve, and his persistent SHPT induced hypercalcemia, hypophosphatemia, and severe bone loss. Thereafter, in December 2007 and July 2013, he underwent 2nd and 3rd parathyroidectomy for removing the swollen PTGs in his left forearm, but the PTH value could not be reduced.

In November 2013, he was admitted to our hospital at age 63 years because of general fatigue and pain in his extremities. His medical history, except for ESRD and SHPT, included chronic hepatitis C (HCV), irritable bowel syndrome (IBS), and a mild degree of aplastic anemia (AA). He had been diagnosed with HCV in 1993 and received interferon therapy just before RT. The mild AA had been diagnosed by bone marrow biopsy in August 2013, after which he underwent blood transfusion at regular intervals in addition to receiving a high dose of darbepoetin (18,000 units per month). His oral medications included low-dose prednisolone (PSL) (5 mg/day), CyA, MMF, losartan, mosapride for IBS, and menatetrenone for bone loss. He had no history of alcohol consumption or smoking. His family medical history was unremarkable.

On admission, his temperature was 36.2°C, his pulse rate was 58 beats per minute, and his blood pressure was 98/62 mmHg. Physical examination findings were unremarkable, except for pain in the extremities. Laboratory tests revealed the following results: white blood cell count, 4,500/mm³; erythrocyte count, 258 × 10⁶/µL; hemoglobin (Hb), 8.4 g/dL; hematocrit, 25.7%; platelet count, 40.3 × 10⁴/mm³; albumin, 4.0 g/dL; blood urea nitrogen, 42.8 mg/dL; creatinine (Cr), 2.7 mg/dL; eGFR, 19.8 mL/min; calcium (Ca), 10.4 mg/dL; phosphorus (P), 3.2 mg/dL; intact-PTH (i-PTH), 756 pg/mL; 25-(OH)D, 13.4 ng/mL (reference range: 9.0-37.6 ng/mL), 1,25-(OH)₂D, 34.5 pg/mL (reference range: 20-60 pg/mL); alkaline phosphatase, 424 IU/L; aspartate aminotransferase, 21 IU/L, alanine aminotransferase 19 IU/L, and C-reactive protein, 0.1 mg/dL. Bone turnover markers showed the following results: bone alkaline phosphatase (BAP), 49.7 µg/mL (reference range: 2.9-14.5 pg/mL); undercarboxylated osteocalcin 48.0 ng/mL (reference range: <4.5 ng/mL); tartrate-resistant acid phosphatase type 5b (TRAP-5b), 931 mU/dL; N-telopeptide of type I collagen, 104/µm²; and collagen type I N-terminal propeptide (P1NP), 548 ng/mL (reference range: 8-39 ng/mL).

Bone dual-energy X-ray absorptiometry (DEXA) in the non-shunt side showed low BMD (T-score, -4.9). In particular, the bone mineral density (BMD) of the femoral neck and distal radius on the non-shunt side by dual-energy X-ray absorptiometry (DEXA, QDR-Discovery; Hologic, Inc., Waltham, MA, USA) showed low levels (0.679 and 0.481 g/cm², respectively). Head CT and MRI showed no intracranial lesions, and there was no evidence of space-occupying lesions (9.3 mm in maximum diameter) with abundant blood flow detected in the left forearm (Fig. 2A, B). The Casanova test (Schlosser et al. 2004) indicated that those left forearm lesions caused excessive...
secretion of PTH. Furthermore, scintigraphy with Tc-99 m labeled methoxy-isobutyl-isonitrile (MIBI) demonstrated intense uptake in the left forearm. Based on these findings, the patient was diagnosed as having severe bone loss due to high bone resorption induced by persistent SHPT in the left forearm. Parathyroid intervention therapy such as parathyroidectomy and PEIT against the left forearm lesions was again considered, but the patient resolutely refused to undergo either of the procedures.

In this difficult clinical situation, subcutaneous administration of 60 mg DMAb was performed. At almost the same time, alfacalcidol (ALF) at a dose of 0.25 μg/day and
Ca lactate at a dose of 3.0 g/day were prescribed to avoid severe hypocalcemia. However, in the 8 days following DMAb administration, the albumin-adjusted serum Ca (adj-Ca) level suddenly decreased to 7.3 mg/dL (Fig. 3) with limb paresthesia and QT prolongation on electrocardiography. Similarly, the P level also decreased to 2.0 mg/dL (Fig. 3). Furthermore, the i-PTH level showed an elevation to 897 pg/mL on day 27 after administration of DMAb, and the i-PTH level reached a peak at 934 pg/mL on day 48 (Fig. 3). To prevent further progression of hypocalcemia, intravenous Ca gluconate was administered for 7 days, and calcitriol at a dose of 1.0 μg/day was prescribed orally instead of ALF. Subsequently, the adj-Ca level recovered to normal range, and the i-PTH level decreased to 393 pg/mL on day 68 after administration of DMAb (Fig. 3). On the other hand, the bone turnover markers sharply decreased after the start of therapy. TRAP-5b and BAP returned to normal (119 mU/dL and 14.3 μg/mL, respectively) on day 48 after administration of DMAb (Fig. 3). Also, the BMD at the femoral neck and distal radius on day 37 improved to 0.498 and 0.453 g/cm², respectively. Furthermore, on day 70 after administration of DMAb, the patient agreed to undergo the 4 th parathyroidectomy for removing the remaining several PTGs in his left forearm. Pathological examina-
tion of the resected biggest PTG showed that it was compatible with single nodular or adenoma-like parathyroid hyperplasia (Wada et al. 2008). Pathological examination further demonstrated a single markedly enlarged nodule of uniform parenchymal cell proliferation resembling an adenoma (Fig. 4). Thereafter, the i-PTH level further decreased to 129 pg/mL on day 160 after administration of DMAb (Fig. 3), and the BMD at the femoral neck and distal radius on day 128 showed gradual improvement to 0.503 and 0.459 g/cm², respectively. Eventually, the adj-Ca, P, BAP, and TRAP-5b levels were maintained within normal range with the administration of calcitriol at a dose of 0.5 μg/day (Fig. 3), which resulted in improvement of the patient’s extremity pain. Additionally, the patient’s renal function remained stable without deterioration. The current serum Cr level and eGFR are 2.6 mg/dL and 21.1 mL/min, respectively. On the other hand, in terms of the improvement of anemia, our patient could not maintain the optimum Hb level suggested by the guideline (Tsubakihara et al. 2010) without blood transfusion, even after the resolution of SHPT.

Discussion

In the present case, several factors including age, corticosteroids for immunosuppressive therapy, and slowly progressive deterioration of graft function were involved in the pathogenesis of bone loss. In particular, nearly ten years of corticosteroid therapy was considered to exert a strong influence on the bone tissue. However, it is evident that persistent and therapy-resistant SHPT also played a central role in the progression of the patient’s severe bone loss. According to previous studies, the risk for developing persistent SHPT after RT increases with the duration of dialysis and the magnitude of SHPT in the pre-renal transplant period (Messa et al. 1998; Douthat et al. 2012). Our patient had been undergoing HD for 34 years and suffering from severe SHPT for 12 years before RT. In addition, severe change in the PTGs, such as monoclonal nodular hyperplasia in the present case, is also known as a main causal factor for persistent SHPT (Messa et al. 1998; Lewin and Olgaard 2006; Douthat et al. 2012). Furthermore, the presence of such monoclonal nodular hyperplasia is closely related to therapy-resistant SHPT. In previous reports, adenomatous monoclonal nodular hyperplasia showed a high proliferative activity and contained a low density of the VD receptor and Ca-sensing receptor, whose specific features engendered resistance to pharmacologic or surgical interventions (Lewin and Olgaard 2006; Wada et al. 2008). Our patient had all of those reported risk factors, which was considered to be attributable to his persistent and therapy-resistant SHPT.

In the management of persistent SHPT after RT, parathyroidectomy has been regarded as the gold standard (Messa et al. 1998; Douthat et al. 2012). However, recurrence of SHPT can occasionally be seen even after appropriate parathyroidectomy. In the present case, such frequent recurrence had increased the patient’s burden and eliminated his desire for repeat surgical intervention. Furthermore, the therapeutic options in place of parathyroidectomy are limited (Cohen et al. 2012; Evenepoel et al. 2014). Indeed, treatment with VD is difficult for patients with persistent SHPT since hypercalcemia is commonly seen in those patients. On the other hand, several studies have suggested that cinacalcet (CIN) offers a new treatment strategy for renal transplant recipients with persistent SHPT (Cohen et al. 2012; Evenepoel et al. 2014). A recent meta-analysis of 21 nonrandomized studies, including a total of 411 renal transplant recipients with persistent SHPT, showed that CIN enabled correction of hypercalcemia and decreased the PTH levels in those patients (Evenepoel et al. 2014). However, CIN is not yet approved as a therapeutic medication for persistent SHPT in renal transplant recipients. In addition, any immediate effects of CIN on severe bone loss in this population remain unknown. Furthermore, various forms of gastrointestinal intolerance including nausea, vomiting, abdominal discomfort, and diarrhea are seen as its common adverse events (Evenepoel et al. 2014), causing CIN to be not recommended for patients with IBS, such as our patient. These concerns led us to abandon the idea of prescribing CIN for our patient.

To date, only a few small studies have shown the effects of DMAb in CKD patients, and no previous report exists regarding DMAb therapy in renal transplant recipients. Moreover, there is no strong evidence to support its efficacy. However, a clinical study by Block et al. (2012) indicated that treatment with DMAb resulted in rapid reduction of bone turnover markers in patients with CKD, which was sustained from the first observation at day 2 to the end of the study at day 113. In addition, Jamal et al. (2011) showed that DMAb is effective in improving the BMD of patients with CKD in a short period of time. Moreover, Chen et al. (2014) showed that DMAb is effective in restor-
ing BMD and reducing bone pain in HD patients with SHPT. Similarly, in the present case, bone turnover markers sharply decreased after the start of DMAb; those levels had been maintained within normal range for a long time. In addition, the patient’s BMD also exhibited improvement in a short period of time before the 4th parathyroidectomy. As far as we know, these rapid improvements cannot be achieved by treatment with parathyroidectomy or CIN (Lewin and Olgaard 2006; Evenepoel et al. 2014). Therefore, we consider that DMAb has a rapid effect in recovery from bone loss with high bone resorption due to SHPT in patients with CKD. However, further studies are necessary to evaluate the long-term effects of DMAb on bone metabolism in CKD patients, especially the influence of DMAb on adynamic bone disease, which could be worsened by anti-bone resorative therapies such as DMAb.

Next, we address the hypocalcemia induced by DMAb in patients with CKD. Previous studies reported that hypocalcemia was the most common adverse effect of DMAb (Jamal et al. 2011; Chen et al. 2014). In addition, recent studies showed that treatment with DMAb induced severe hypocalcemia in CKD patients (particularly, CKD stage 4-5D patients complicated with SHPT) compared to the general population (Jamal et al. 2010; Dave et al. 2015). Furthermore, DMAb-induced hypocalcemia was demonstrated to develop during the first two weeks of DMAb administration in CKD patients (Block et al. 2012). Our patient showed hypocalcemia in the 8 days following DMAb administration. Also, in other previously reported cases regarding DMAb therapy for CKD patients, severe hypocalcemia was observed just after administration (Talreja 2012; McCormick et al. 2012; Torregrosa 2013; Agarwal et al. 2013; Ungprasert et al. 2013; Farinola and Kanjanapan 2013). Furthermore, clinical studies by Chen et al. (2014, 2015) indicated that hypocalcemia was corrected shortly after adjusting Ca intake, VD dosage and Ca dialysate in HD patients with SHPT. Therefore, we consider that DMAb-induced hypocalcemia can be prevented with up-titration of the VD dosage and Ca supplementation. Concomitantly, we suggest the importance of careful monitoring of the serum Ca level during the DMAb therapy (at least several months) to achieve strict control of the Ca level. Such monitoring could be effective in preventing the occurrence of serious side effects, including not only hypocalcemia but also rebound hypercalcemia, as a result of intensive VD treatment.

As described above, the presence of severe renal dysfunction increases the risk of DMAb-induced hypocalcemia, but conversely, administration of DMAb might be considered to safely allow intensive use of VD in advanced CKD patients. In other words, DMAb therapy may provide a therapeutic option to prescribe a more aggressive dose of VD, enabling control of SHPT in this population. In fact, our patient showed a quick reduction in his i-PTH level before the 4th parathyroidectomy as a result of intensive VD treatment, which was originally prescribed for correcting hypocalcemia. Furthermore, a recent open-label study (Chen et al. 2015) regarding the effects of DMAb on HD patients with severe SHPT showed interesting results. In that study, the combination of DMAb and VD led to not only a rapid improvement in BMD, but also a decrease in the i-PTH level and parathyroid gland volume (Chen et al. 2015). Therefore, we suggest that the combination of DMAb and high-dose VD might have therapeutic potential for controlling severe SHPT. Accordingly, we expect this combination therapy to provide another therapeutic option for patients who are poor candidates for parathyroidectomy or CIN therapy.

In conclusion, DMAb itself does not exert any direct effects on PTGs, but treatment with DMAb was effective in improving bone loss in a short period of time. In addition,
administration of DMAB allowed the administration of high-dose VD, which ultimately enabled control of SHPT and prevented hypocalcaemia induced by DMAB. Therefore, the combination of DMAB and high-dose VD might be a reasonable approach for reversing severe osteoporosis due to therapy-resistant SHPT in patients with CKD by compensating each other’s disadvantage about Ca balance. However, accumulation of similar cases is needed to establish strong evidence, and further studies will also be important to elucidate whether this combination can improve the long-term prognosis in these patients.

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Conflict of Interest

The authors declare no conflict of interest.

References


Tsubakihara, Y., Nishi, S., Akiba, T., Hirakata, H., Iseki, K.,...
