An Open-Label, Prospective Pilot Clinical Study of Denosumab for Severe Hyperparathyroidism in Patients With Low Bone Mass Undergoing Dialysis

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Context: Denosumab is widely used for bone diseases with increased bone resorption. Its effectiveness in patients with severe secondary hyperparathyroidism on dialysis is unclear.

Objective: This study aimed to evaluate the efficacy and safety of denosumab in patients with severe secondary hyperparathyroidism who are on dialysis.

Design: This 6-month prospective, open-labeled study evaluated 12 patients (five women, seven men; mean age 53.5±3.8 y). All had intact PTH (iPTH; > 1000 pg/mL), low bone mass (T-score < −1.0 SD), and bone pain and were poor surgical candidates. Serum calcium, phosphorus, alkaline phosphatase (AP), and iPTH levels were assessed at baseline and every month thereafter. Vertebral spine x-rays and bone mineral densities (BMDs) (lumbar spine and femoral neck) were assessed at the start and end of the study. All patients received denosumab (60 mg), calcitriol, phosphate binders, and dialysate calcium that were adjusted according to the biochemistry data.

Results: The BMD increased in both the femoral neck (mean increase 23.7% ± 4.0%) and lumbar spine (17.1% ± 2.6%) after 6 months. In the first month, most patients had increased iPTH levels, which dramatically decreased from 1702.1 ± 181.9 to 518.8 ± 126.8 pg/mL by the end of the study after increasing the calcitriol dose. All patients had significant decreases in AP, calcium × phosphorus, and bone pain. Changes in femoral neck BMD correlated only with AP and iPTH levels.

Conclusions: Denosumab is effective in restoring bone mass and reducing bone pain in patients on dialysis with secondary hyperparathyroidism. It also allows for a more aggressive use of calcitriol to control hyperparathyroidism. (***J Clin Endocrinol Metab*** **99: 2426–2432, 2014)**

The definition of chronic kidney disease mineral and bone disorder (1), including secondary hyperparathyroidism (SHP), is used to describe the wide range of systemic mineral metabolism derangements. SHP is one of the main complications in patients with end-stage renal disease (ESRD) and affects most patients receiving dialysis (2). Secondary hyperparathyroidism, a disorder characterized by elevated serum PTH levels, stimulates bone demineralization and contributes to calcium and phosphorus efflux from the bone that may impact cardiovascular health through hypercalcemia, hyperphosphatemia, and vascular calcification (3, 4). Low-calcium dialysate, which reduces hypercalcemia, thereby prevented the artery calcification and significantly decreased bone min-

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Abbreviations: AP, alkaline phosphatase; BMD, bone mineral density; DEXA, dual-energy X-ray absorptiometry; ESRD, end-stage renal disease; iPTH, intact PTH; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor-κB ligand; SHP, secondary hyperparathyroidism.

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eral density (BMD) in ESRD patients (5). Moreover, there is an increasing incidence in the elderly dialysis patients that is associated with a higher risk of low bone mass.

Treatment with oral or iv calcitriol can decrease intact PTH (iPTH) levels and improve bone histology (6). However, patients with renal failure receiving dialysis are at an increased risk of developing hypercalcemia, hyperphosphatemia, and vessel calcification. Although SHP can be controlled medically in most patients, management may be difficult if hypercalcemia and hyperphosphatemia are present, and parathyroidectomy is an alternative treatment of these patients. Unfortunately, many patients with ESRD are poor surgical candidates because of their cardiovascular and functional status and multiple comorbidities.

Although the therapeutic options for secondary hyperparathyroidism have broadened in recent years, there is still no currently approved therapy that can compensate for the long-term calcium and phosphate loss from the bone or that can restore normal bone integrity in most patients with secondary hyperparathyroidism and very low bone mass. Cinacalcet, a novel calcium-sensing receptor agonist, has been evaluated but with controversial results (7, 8). Attempts to combine therapies with different mechanisms of action to increase therapeutic effectiveness has achieved limited success. Parathyroidectomy has been reported to result in an increase of only 10% in bone mass after 1 year (9, 10).

Denosumab (Prolia; Amgen Inc) is a fully human monoclonal antibody that acts as an osteoprotegerin (OPG) mimicker directed against the receptor activator of nuclear factor-κB ligand (RANKL), which interferes with the formation and survival of osteoclasts. It has been approved by the Food and Drug Administration in June 2010 as a new treatment for postmenopausal osteoporosis in women who are at high risk of fractures (11, 12). It is the antiresorptive therapy for osteoporosis that could be safe and efficacious in patients with renal impairment (13). Furthermore, the RANKL inhibitor OPG has been proven as a bone-protective agent in a rat model of chronic renal insufficiency and hyperparathyroidism (14). Denosumab therefore may be useful in managing serum calcium levels and preventing bone loss in such patients.

This antiresorptive therapy has been used in combination with high-dose calcitriol for secondary hyperparathyroidism to selectively decrease osteoclast function, thereby widening the therapeutic window of calcitriol and potentially achieving maximum bone mass and hyperparathyroidism control. The aim of this study was to evaluate the efficacy and safety of denosumab in dialysis patients who were affected by severe secondary hyperparathyroidism and low bone mass and were receiving oral calcitriol.

Materials and Methods

Study design

This 24-week, open-label, single-dose, outpatient study was conducted at Kaohsiung Veterans General Hospital. The hospital's institutional review board approved this study, which was conducted in accordance with the principles of the Declaration of Helsinki. Each participant provided written informed consent.

Subjects receiving regular peritoneal dialysis or hemodialysis were screened for eligibility up to 21 days before entry into the study, whereas baseline evaluations were conducted on the day before the study treatment. The study protocol included requirements for daily calcium and calcitriol supplementation according to standard dialysis guidelines (1) for subjects with ESRD with an iPTH level greater than 1000 pg/mL. All of the patients had been receiving renal replacement therapy for at least 3 years and had various degrees of osteopenia with bone mineral densities, which were measured by dual-energy X-ray absorptiometry (DEXA); furthermore, all patients had a femoral neck or lumbar spine T score lower than −1.0 SD, indicative of low bone mass (15). The inclusion criteria were aged older than 18 years, stable laboratory tests during the 6-months period prior to the study for this degree of renal dysfunction and hyperparathyroidism, and baseline clinically acceptable physical examination and electrocardiograph results at screening. The exclusion criteria were as follows: known sensitivity to any study treatment, any unstable medical condition, a history of malignancy, active infection, pregnancy, lactating/nursing, and known alcohol or drug abuse at screening.

The eligible subjects received a single 60-mg sc dose of denosumab (Prolia; Amgen, Inc) at the start of the 6-month study period. Concomitant medications included acetaminophen, vitamins, topical medications, and treatments for renal disease or associated conditions. None of the patients received cholecalciferol or ergocalciferol during the study. The patients returned for follow-up visits on days 7, 14, and 21 and every month thereafter. In addition to recording of adverse events at each visit, predialysis blood samples for measurement of serum calcium, phosphorus, alkaline phosphatase (AP) and iPTH levels were obtained for hemodialysis patients, whereas standard blood samples were collected from peritoneal dialysis patients. A visual-analog bone pain scale from 0 to 10 was used for evaluation at each follow-up visit.

During the study, the patients followed a dialysis schedule of 4 hours per session thrice a week or a daily peritoneal dialysis schedule. The patients received denosumab in combination with calcitriol (1 μg/d), calcium carbonate (3 g/d), and dialysate calcium of (3 mEq/L) at the start of the study that were titrated according to the serum calcium levels until the end of the study. The serum iPTH level was measured by an immunoradiometric assay (Nichols Institute Diagnostics) with a normal range between 12 and 65 pg/mL. Serum levels of calcium, phosphorus, and AP were measured using standard methods.

The BMD was measured using Hologic Discovery DEXA scanner (Hologic Inc). The scans covered four lumbar vertebrae (L1-L4) and the proximal femur. The results were expressed as grams per square centimeter and derived by dividing the bone mineral content of the hydroxyapatite of each region by the projected bone area. To overcome intrapatient measurement errors, we used the Hologic scanner that could automatically adjust for

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body size and performed the procedure in a standard body position. The data were analyzed using in-hospital least significant change values (spine 0.022326 g/cm^2; femoral neck 0.026675 g/cm^2). In addition, we recruited eight control patients who did not receive denosumab but otherwise fulfill the inclusion criteria to rule out any methodological bias. Changes in BMD values were correlated with the initial data collected before the treatment (vitamin D status, calcium, phosphorus, AP levels, age, body weight, and iPTH levels).

Statistical analyses

The outcomes of interest were the changes in BMD, calcitriol dose, serum calcium, phosphorus, AP, and iPTH levels. Statistical analysis was performed using statistical software SPSS version 13. All of the results are expressed as the mean and SEM. For measuring differences between two groups, ordinal demographic data were evaluated using the χ^2 test or the Fisher's exact test, as appropriate, whereas continuous data were evaluated using the Mann-Whitney *U* test. For differences within the same group, the nonparametric Wilcoxon signed-rank test was used when assumption of normal distribution was violated. Nonparametric Spearman correlation analyses were conducted to evaluate bone densitometry changes. All tests were two tailed and significance was set at $P < .05$.

Results

Twelve patients with severe secondary hyperparathyroidism and low bone mass were evaluated. The mean age at the time of denosumab administration was 53.5 ± 3.8 years, and the time after beginning dialysis was 158.5 ± 20.3 months. The causes of ESRD were chronic interstitial nephritis due to the use of herbal drugs (n = 5), chronic glomerulonephritis without biopsy (n = 2), a failed renal transplant (n = 1), diabetes nephropathy (n = 1), polycystic kidney disease (n = 1), chronic pyelonephritis (n = 1), and IgA nephropathy (n = 1). Parathyroidectomy was indicated for all patients with a serum iPTH level greater than 1000 pg/mL and image-proven renal osteodystrophy with bone pain. However, surgery was not an option because of the high risks of cardiovascular mortality (n = 4), suspected parathyromatosis (n = 2), and patient refusal (n = 6).

The DEXA studies of the patients revealed femur neck (0.57 ± 0.04 g/cm^2, T score −2.81 ± 0.38 SD) and lumbar spine (0.81 ± 0.04 g/cm^2, T score −1.78 ± 0.35 SD). The vitamin D status of the study group revealed the serum levels of 25-hydroxyvitamin D as 35.9 ± 4.1 ng/mL. In addition to the above baseline data, the counterpart results of the control group are presented in Table 1.

Figure 1 shows the kinetics of serum calcium, phosphorus, iPTH, and AP levels, calcium × phosphorus product, and calcitriol during the 6 months' periods prior to and after the study. There was a slight drop in serum calcium in the first months with a nadir of low calcium levels was detected in the first 2 weeks, which increased after increased calcitriol dosages (Figure 1A). There were similar trends in serum phosphorus (Figure 1B) and calcium × phosphorus (Figure 1C) through the study period. There was a significantly increased calcitriol dosage in the first 3 months that was decreased because of higher serum calcium levels (Figure 1D). The kinetics of iPTH and AP revealed a peak iPTH value in most patients in the first month of denosumab therapy and reversed PTH levels after increased calcitriol doses (Figure 1, E and F). There were also significantly decreased changes in AP. The patients' hyperparathyroidism dramatically decreased from the initial iPTH of 1702.1 ± 181.9 pg/mL to 518.8 ± 126.8 pg/mL after completing the study.

The BMD and bone pain score changes are shown in Figure 2, which revealed that BMD significantly improved at the end of the study period, with mean increase in femoral neck BMD of 23.7% ± 4.0% from the initial 0.57 ± 0.04 g/cm^2 to 0.72 ± 0.05 g/cm^2 (Figure 2A) and mean increase in lumbar spine BMD of 17.1% ± 2.6% from the initial 0.81 ± 0.04 g/cm^2 to 0.94 ± 0.05 g/cm^2 (Figure 2B). The counterpart results of the control group revealed no significant changes in femoral neck BMD with the initial 0.61 ± 0.04 g/cm^2 to 0.63 ± 0.04 g/cm^2 (Figure 2A) and

Table 1. Demographic Data and Characteristics of the Dialysis Patients Recruited in This Study

	Hyperparathyroidism With Low Bone Mass Patients	Control Group	*P* Value
Case numbers	12	8	
Sex (female/male)	5/7	3/5	1.000
Body weight, kg	56.0 ± 2.3	59.5 ± 3.7	.140
Hemodialysis/peritoneal dialysis	11/1	6/2	.537
Duration of dialysis, mo	158.5 ± 20.3	99.5 ± 19.6	.060
iPTH, pg/mL	1702.1 ± 181.9	1300.1 ± 132.1	.175
AP, U/L	449.8 ± 94.2	330.1 ± 81.3	.461
Calcium, mg/dL	10.1 ± 0.4	10.1 ± 0.3	.414
Phosphorus, mg/dL	5.3 ± 0.3	6.0 ± 0.3	.278
Femoral neck, g/cm^2	0.57 ± 0.04	0.61 ± 0.04	.305
Lumbar spine, g/cm^2	0.81 ± 0.04	0.90 ± 0.09	.427

Data are expressed as mean ± SEM.

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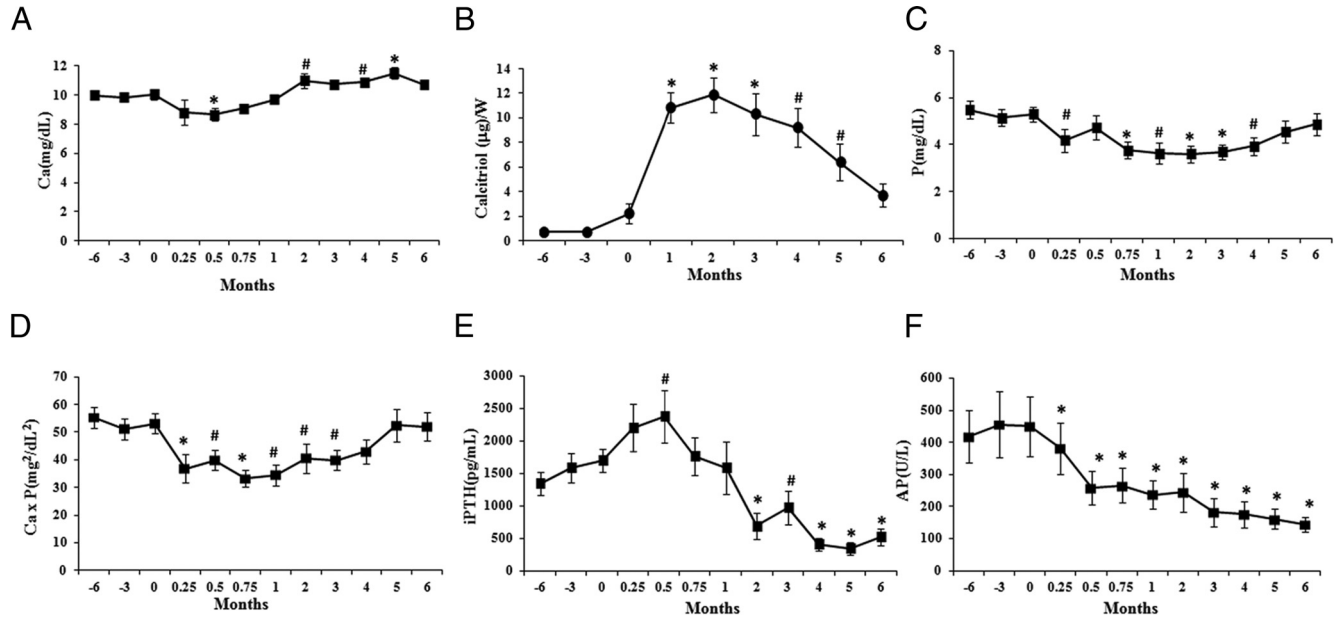

Figure 1. Changes in serum total calcium levels (A), calcitriol dosages (B), phosphorus (C), calcium × phosphorus (D), iPTH (E), and AP (F) before and after denosumab treatment. Ca, calcium; P, phosphorus. #, $P < .05$; *, $P < .01$.compared with the day 0 data of the patients.

no significant changes in lumbar spine BMD from the initial 0.86 ± 0.05 g/cm^2 to 0.87 ± 0.05 g/cm^2 (Figure 2B).

The bone pain also significantly improved (Figure 2C). The changes in BMD of the participants correlated with initial treatment data of age, body weight, AP, iPTH, and PTH changes after completing the study. Only serum AP and iPTH levels significantly correlated with BMD improvement (Table 2).

The most common adverse events were hypocalcemia (Table 3). Calcium carbonate, calcitriol, and dialysate (3.0 mEq/L) supplementation was initially required by the study protocol. However, this was increased to high calcium dialysate (3.5 mEq/L) during the study. Four subjects of the eight patients had nadir serum calcium levels of greater than 6 and less than 7.0 mg/dL with the original protocol. Hypocalcemia improved by adjusting the calcium intake, dialysate calcium level, and calcitriol dosage. None of the four subjects who received adequate calcium (3–4 g/d) and calcitriol (2 μg/d) supplementation and appropriate high-calcium dialysate (3.5 mEq/L) had symptomatic hypocalcemia (<7.5 mg/dL). We did not observe any hypocalcemia, osteonecrosis of the jaw, or infections that required hospital admissions during or after the administration of denosumab.

Discussion

The patients in the study had very high levels of PTH, Ca × P products and alkaline phosphatase, suggesting hyperparathyroidism with high-turnover bone disease. Bone densitometry values and serum alkaline phosphate levels improved with a decrease in PTH levels after treatment. There were acceptable calcium abnormalities that were attributable to the concomitant use of a calcium dialysate bath and supplementation with calcium tablets and calcitriol, which would have resulted in the up-regulation of the gastrointestinal absorption of calcium to counter the influx of calcium to the bone. The results suggest that denosumab therapy may provide a wider therapeutic window to allow for a more aggressive use of calcitriol to control hyperparathyroidism. There is also an offsetting

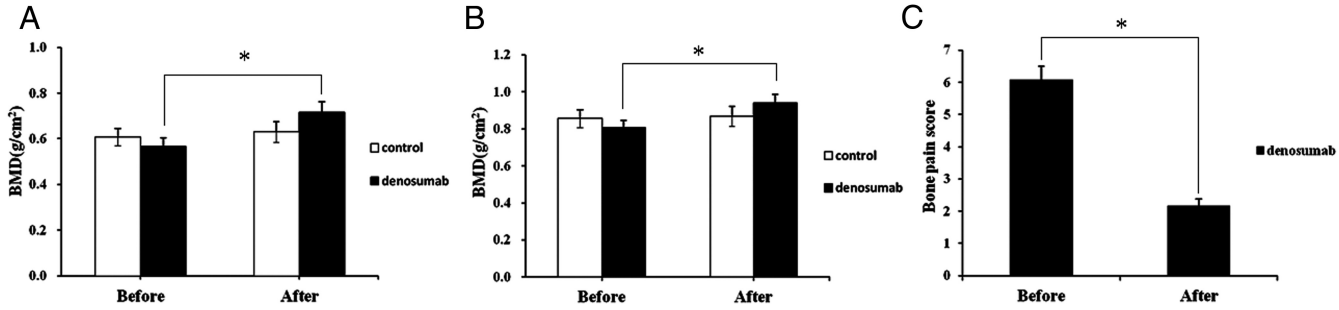

Figure 2. Changes in femoral neck (A) and vertebra BMD (B) and pain scores (C) before and after denosumab treatment. #, $P < .05$; *, $P < .01$.

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Table 2. Correlation of Improvement in Femoral Neck BMD in Dialysis Patients With Severe SHP and a Low Bone Mass

Factors of the Patients Before Treatment	Correlation Coefficient
Age, y	−0.554
Body weight	0.294
iPTH, pg/mL	0.771[a]
Calcium, mg/dL	−0.140
Phosphorus, mg/dL	0.245
AP, U/L	0.713[a]
25-Hydroxyvitamin D, ng/mL	−0.403
iPTH reduction percentage (before and after denosumab)	−0.070

[a] $P < .01$.

effect on calcium and phosphate that may reduce the risk of hypercalcemia and hyperphosphatemia that could accompany high-dose calcitriol therapy. Moreover, the combination of high bone turnover hyperparathyroidism and therapy with denosumab also rapidly ameliorated bone pain.

Bisphosphonates are stable pyrophosphate analogs that act mainly by promoting osteoclast apoptosis and therefore decreasing bone resorption and subsequent bone remodeling. Their efficiency is well established in patients without renal insufficiency with respect to increasing BMD, decreasing new fracture rates, and preventing corticoid-induced osteoporosis (16). The fact that bisphosphonates are either bound to bone and stored in the skeleton for years, or excreted intact via the kidney, has led to an ongoing debate regarding their long-term safety and their use in renal impairment (17). Denosumab, approved in 2010 for the treatment of osteoporosis, is administered as a sc injection twice a year. It is gaining popularity in primary care due to its ease of administration and no need for dose adjustment in patients with decreased kidney function (18). Denosumab potentially offers another important advantage compared with bisphosphonates because it is degraded within 3–4 months after injection and hence does not remain in the body (19). The most common adverse effect associated with denosumab is hypocalcemia. Similar to the side effects for bisphosphonates, there is also a possibility for an increased risk for adynamic bone disease and jaw osteonecrosis. To reduce these risks, we chose patients with high-turnover bone disease because of the very high serum levels of iPTH and AP in these patients.

All of the patients in the current study presented with extremely low bone mass, bone pain, and severe secondary hyperparathyroidism. After conservative treatment with denosumab and calcitriol has improved these conditions. An increase in BMD greater than 20% after 6 months of treatment with this antiosteoporotic drug is a quite unexpected observation in adults. The important issue is whether the observed BMD results represent a biological function or methodological bias. The data were analyzed using in-hospital least significant change values. At the same time, we recruited eight ESRD patients who did not have significant changes of BMD in the 6 months. Based on these observations, the results should be attributed to the effects of denosumab in selectively inhibiting the function of osteoclasts with minimal changes of osteoblastic function. Thus, denosumab may play a role in the treatment of high turnover bone disease in hemodialysis patients. A meta-analysis suggested that BMD was lower in patients with stage 5 chronic kidney disease who have fractures (20). The improvement in bone mass was positively correlated with high bone turnover markers such as iPTH and AP levels (Table 2). This means that higher bone turnover by selectively arresting of osteoclast function while simultaneously maintaining osteoblast function could provide the patients with the maximum bone mass gain. It is reasonable to expect that this therapy would deliver benefits of increased bone mass in severe hyperparathyroidism. Furthermore, denosumab possibly im-

Table 3. Initial PTH Levels of and Treatment Given to Individual Patients

Case Number	iPTH, pg/mL	Calcium, mg/dL	AP, U/L	Nadir of Serum Calcium, mg/dL	Calcium Carbonate, g/d	Calcitriol Dosage, μg/d	Dialysate Calcium, mEq/L
1	1007	9.8	117	8.9	3	1	3
2	1359	10.9	197	6.7	3	1	3
3	1190	8.2	197	6.6	3	1	3
4	1606	9.7	198	8.1	3	1	3
5	1552	9.1	863	6.9	3	1	3
6	1016	13.5	73	9.8	3	1	3
7	3083	9.3	499	6.3	3	1	3
8	2007	9.3	723	8.0	3	1	3
9	1159	10.3	142	7.9	3	2	3.5
10	1880	10.1	716	8.0	3	2	3.5
11[a]	2283	10.2	923	7.8	4	2	3.5
12	2283	10.2	750	9.1	3	2	3.5

[a] Case 11 was under continuous ambulatory peritoneal dialysis.

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proves bone quality as evidenced by its effect on osteoprotegerin as a bone-protective agent in a rat model of chronic renal insufficiency and hyperparathyroidism (14). It is possible that treating patients with low BMD and renal osteodystrophy by correcting vitamin D deficiency and controlling hyperparathyroidism can improve their bone health and reduce their risk of fractures.

There are few studies on the use of denosumab in patients with ESRD. However, it would be reasonable to use denosumab in dialysis patients to treat high bone turnover hyperparathyroidism because PTH concurrently stimulates RANKL expression and inhibits OPG production by osteoblasts and thus promotes osteoclastogenesis. OPG, acting as a RANKL inhibitor can inhibit PTH-mediated osteoclastogenesis and decrease bone turnover (14). Denosumab, with its OPG mimicking activity has the same effects. On the other hand, a combination of denosumab with calcitriol also would be reasonable because the development of hypercalcemia often prevents adequate calcitriol therapy or because the development of hungry bone syndrome prevents denosumab therapy. Patients on dialysis are at increased risk for developing high bone turnover due to secondary hyperparathyroidism. In these patients, the early and rapid suppression of bone resorption, promoted by denosumab, with the yet-unchanged bone formation rate may decrease serum calcium concentrations with a compensatory increase in iPTH secretion, as was seen in the first month. The increased dose of calcitriol permitted control over this increase in iPTH secretion and was able to partially normalize it with a nonhypercalcemia effect. In this study, the initial iPTH levels of 1702.1 ± 181.9 pg/mL dramatically decreased to 518.8 ± 126.8 pg/mL after 6 months. This therapy could be a bridge for severe hyperparathyroidism with very low bone mass before parathyroidectomy to improve bone mass gain and possibly decrease the incidence or severity of hungry bone syndrome or could be a rescue therapy to control hyperparathyroidism in patients who are poor candidates for parathyroidectomy. Finally, because the serum iPTH level might elevate at 6 months, cinacalcet would be a potentially useful addition to the management of hyperparathyroidism.

As illustrated in these cases, the low bone mass and hyperparathyroidism in patients followed by the rapid improvement in BMD, bone pain, and a reduction of PTH levels further emphasizes the value of this treatment. There were significant reductions in serum phosphorus, Ca × P product, and serum AP between the baseline and the end of the study. Surprisingly, there was a significant decrease in the levels of Ca × P in the denosumab group in our study, when in fact the serum calcium level increased significantly. This may be partly explained by the fact that, in clinical practice, serum phosphorus levels usually decrease by a higher factor compared with serum calcium levels and are therefore the greater culprit in causing the lower Ca × P product in these patients with SHP and low bone mass who receive a calcitriol and denosumab treatment regimen to avoid vessel calcification.

Studies attesting to the safety of denosumab for hemodialysis patients consist of a preliminary report of eight patients who received a single injection of denosumab (13). According to our study, four of the eight patients had a nadir serum calcium level of greater than 6 and less than 7.0 mg/dL with the original protocol (dialysate calcium 3.0 mEq/L) and calcitriol treatment (1 μg/d) in the first to second week. Hypocalcemia was improved soon upon adjustment of calcium intake and dialysate calcium levels and by administration of high-dose calcitriol. None of the four subjects who received adequate calcium and calcitriol (2 μg/d) supplementation and appropriately high calcium dialysate (3.5 mEq/L) had symptomatic hypocalcemia (<7.5 mg/dL). The calcium balance of patients should be positive because of oral calcium, calcitriol, and dialysate calcium balance (3.5 mEq/L of free calcium dialysate bath is equal to 14 mg/dL of total calcium levels). No hypocalcemia, osteonecrosis of the jaw, or infections requiring hospital admission were observed during or after the administration of denosumab. However, high-dose calcitriol, calcium supplements, high calcium dialysate, and weekly monitoring of serum calcium were suggested in the first month to prevent hypocalcemia.

The current study has some limitations. First, it is a small-sized, open-label pilot study of limited power. A large-scale, randomized controlled trial is necessary to confirm the efficacy of the treatment. Second, bone biopsy with quantitative histomorphorphometric analysis is the gold standard for the diagnosis of renal osteodystrophy. One of the limitations of our study is that we did not perform a bone biopsy to confirm exclusive hyperparathyroid bone disease in our patients. Nonetheless, bone biopsy is an invasive procedure that is not routinely performed. Numerous studies have demonstrated that high-turnover bone disorders, osteitis fibrosa, and mixed uremic osteodystrophy are associated with serum iPTH levels greater than 400 pg/mL (1, 21, 22). The serum level of iPTH, although not as accurate as bone biopsy, is a reasonably reliable predictor of bone histology in dialysis patients. Parathyroidectomy is usually recommended in patients with a serum iPTH level higher than 800 pg/mL (1, 22). Although not confirmed by bone biopsy, all of our patients had serum iPTH level greater than 1000 pg/mL, which predicts severe SHP.

In conclusion, denosumab represents a potentially useful tool for dialysis patients with severe secondary hyper-

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parathyroidism and low bone mass. Therapy with sc denosumab is effective in controlling hypercalcemia and hyperphosphatemia and allows for a more aggressive use of calcitriol while at the same time dramatically improving the BMD and suppressing SHP in dialysis patients.

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