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Efficacy and Safety of Denosumab for the Treatment of Osteoporosis in Patients with Chronic Kidney Disease

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Abstract

Background: Chronic kidney disease (CKD) is an independent risk factor for osteoporosis and may lead to metabolic abnormalities that accelerate bone loss. Bisphosphonates, the most widely used treatment for osteoporosis, are contraindicated in patients with severe renal impairment. In the present study, we assessed whether denosumab is a safe and effective treatment for osteoporosis in patients with CKD.

Methods and Findings: A total of 143 patients with osteoporosis who were treated with denosumab were analyzed retrospectively. Of these patients, 40 had been previously treated with bisphosphonates. All patients received supplemental vitamin D. Effectiveness was assessed by analyzing changes in bone mineral density (BMD) and serum tartrate-resistant acid phosphatase (TRACP)-5b as a marker for serum bone resorption. More than fifty percent of the patients treated with bisphosphonates showed low BMD at the time their therapy was changed to denosumab. Denosumab was associated with a larger increase in both lumbar and femur neck BMD than were bisphosphonates (+4.8% and +5.5%, respectively). Denosumab decreased serum TRACP-5b while increasing BMD (P<0.001), and was well tolerated. Serum calcium levels decreased shortly after the injection of denosumab, but recovered within 14 days. Supplemental vitamin D (0.5 to 1.0 μg/day) appeared to prevent hypocalcemia and to support efficacy of denosumab.

Conclusions: Denosumab increases BMD in the lumbar vertebra and femur neck in patients with CKD. The effect of denosumab on BMD is greater than that of bisphosphonates in these patients.

Keywords: Denosumab; Bisphosphonates; Osteoporosis; CKD; Corticosteroid

Abbreviations:

BMD: Bone Mineral Density; CKD: Chronic Kidney Disease; eGFR: Estimated Glomerular Filtration Rate; RANK: Receptor Activator of Nuclear Factor-Kappa B; RANKL: Receptor Activator of Nuclear Factor-Kappa B ligand; TRACP-5b: Serum Tartrate-Resistant Acid Phosphatase 5b; YAM: Young Adult Mean.

Introduction

Osteoporosis, which is characterized by low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, is associated with an increased risk of fracture [1]. Bone loss can take place as a result of estrogen deficiency in postmenopausal women, and the risk of fracture correlates with increasing age and decreasing BMD [2].

The incidence of chronic kidney disease (CKD) also increases with age. More than half of individuals older than 70 years have a decreased estimated glomerular filtration rate (eGFR) (<60 mL/min/1.73 m^2) [3]. CKD is an independent risk factor for osteoporosis [4-7]. Individuals with CKD may have an increased risk for osteoporosis for several reasons, including shared risk factors for both conditions such as advanced age and female gender. In addition, CKD may lead to metabolic abnormalities that accelerate bone loss, such as chronic metabolic acidosis, hypogonadism, hyperparathyroidism, and abnormalities of vitamin D metabolism [8]. Osteoporosis can also be induced by glucocorticosteroids, which are widely used as an immunosuppressive agent for glomerulonephritis. Bone loss is a serious side effect of this therapy [9].

Bisphosphonates are the most widely used treatment for osteoporosis. They reduce the risk of fracture in the short term. The critical problem is that there is no evidence of efficacy for long-term treatment [10,11]. Moreover, bisphosphonates may lead to a deterioration of renal function [12]. Thus, bisphosphonates are either not recommended, or contraindicated outright, for use in patients with severe renal impairment [12,13].

The receptor activator of nuclear factor-kappa B ligand (RANKL) is essential in the formation, activation, and survival of osteoclasts [14]. Denosumab binds RANKL with high affinity and specificity, preventing activation of its cognate receptor RANK, which is expressed on the surface of osteoclasts and osteoclast precursors. Inhibition of Signaling through the RANK receptor prevents osteoclast maturation, activation, and survival, thereby decreasing resorption of cortical and trabecular bone [15]. Inhibition of bone resorption with denosumab improves the structural strength of bone [16]. Treatment with denosumab has been associated with significant reductions in fracture risk across a wide range of patient groups [15,17]. Furthermore, long-term clinical trial follow-up data from the FREEDOM study demonstrates that denosumab treatment for up to 8 years is associated with a persistent reduction of bone turnover, continued increases in BMD without therapeutic plateau, and low fracture incidence [18]. It is unknown whether treatment for osteoporosis with denosumab is safe or effective in patients with CKD. In the present study, we examined the efficacy and adverse effects of denosumab treatment in patients with CKD in real-world clinical practice.

Methods

Participants

A total of 143 patients with CKD who had been treated with denosumab were analyzed retrospectively. There were no exclusion criteria based on renal function. However, the patients were excluded if they had not received a second injection within 7 months of the first; this time window (6 months plus a 1-month grace period) represents the coverage period of a denosumab injection. During the study, all the patients concomitantly received vitamin D. This study was approved by the relevant institutional review boards. All patients provided informed consent to allow access to their relevant medical records.

BMD measurement

BMD was measured by dual-energy X-ray absorptiometry (DEXA) at the spine and femur neck before initiation of denosumab and every 6 months thereafter. BMD values were expressed as percent young adult mean (YAM).

Evaluations of clinical data

Patients underwent regular physical examinations, hematological monitoring, blood chemistry measurements, and urine analysis. We included patients whose serum creatinine, albumin-adjusted calcium, phosphate, and alkaline phosphatase had been measured every 3 months. Serum tartrate resistant acid phosphatase (TRACP)-5b was measured every 6 months. Serum TRACP-5b is used as a marker for bone resorption because it is derived from bone-resorbing osteoclasts, and has the advantage of not being influenced by renal dysfunction [19]. All measurements were performed centrally in a single batch at our hospital and at a validated institution (SRL, Tokyo, Japan).

Statistical Analyse

Paired t-tests were used to compare YAM values recorded at baseline with those recorded after every 6 months of treatment with denosumab. Percent changes from baseline in YAM serum markers at each time point were compared with baseline measurements using ANOVA. A significance level of 0.05 was used. All statistical analyses were performed using GraphPad Prism statistical software (Version 5, GraphPad Software, San Diego, CA, USA).

Results

Baseline characteristics

Characteristics of the patients are summarized in Table 1. A total of 143 patients with osteoporosis were enrolled in this study. Patients with each stage of CKD (based on estimated GFR) were included, including hemodialysis patients. Ninety-five patients had received denosumab as the first therapy for osteoporosis, and 40 had received bisphosphonates before their therapy was changed to denosumab.

Table 1: Baseline characteristics. SERM: Selective Estrogen Receptor Modulator; Bis: Bisphosphonates.

Gender	Male 44, Female 99	
Age	19 - 96 years (mean: 65.2 years)	
CKD stage	non-CKD	40
	Stage 2	20
	Stage 3a+3b	46
	Stage 4	23
	Stage 5	8
	Stage 5D	6
Medication	Denosumab: initial therapy	95
	exchange from vitaminD	6
	exchange from SERM	2
	exchange from Bis	40

Osteoporosis was not satisfactorily treated with bisphosphonates

At the time of change from bisphosphonates to denosumab, BMD was measured in each subject (n=40). Surprisingly, more than half of the patients treated with bisphosphonates showed low BMD (less than 70% YAM; Figure 1). In particular, patients treated with a corticosteroid for glomerulonephritis showed low BMD despite bisphosphonate therapy.

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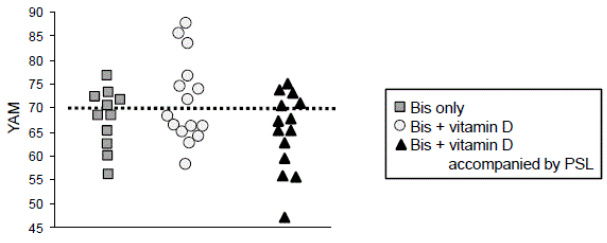

Figure 1: Bone mineral density (BMD) at the time of change from bisphosphonates to denosumab. BMD was measured at the time that the patient switched from bisphosphonates to denosumab (n=40). More than half of the patients treated with bisphosphonates showed low BMD (less than 70% YAM). In particular, the patients treated with corticosteroid for glomerulonephritis showed lower BMD than did patients that were not treated with corticosteroid. Bis: Bisphosphonates.

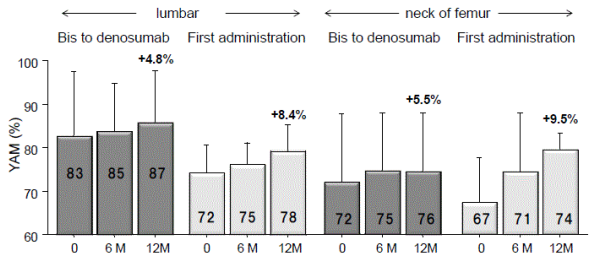

Figure 2: Strong effect of denosumab compared to bisphosphonates. Changes of bone mineral density (BMD) were evaluated in lumbar vertebrae and femur neck after treatment with denosumab. After 12 months of treatment with denosumab, BMD was significantly increased in both lumbar vertebrae and femur neck, +8.4% and +9.5%, respectively. BMD was also increased in cases where the therapy was changed from bisphosphonates to denosumab. Bis: Bisphosphonates.

Denosumab increased BMD more than bisphosphonates did

Changes in BMD were evaluated in the lumbar vertebrae and femur neck after treatment with denosumab. After 12 months of treatment with denosumab, BMD increased in lumbar vertebra and femur neck by +8.4% and +9.5%, respectively (Figure 2). BMD also increased in cases where the therapy was changed from bisphosphonates to denosumab, with the increase in lumbar vertebra and femur neck being +4.8% and +5.5%, respectively (Figure 2).

Denosumab treatment improved bone metabolic markers and was accompanied by persistent increase in BMD

Clinically relevant changes were not seen in serum chemistry, hematology, or urine analyses. No adverse events were reported. During the course of denosumab treatment for 24 months, serum calcium and phosphorus levels did not change significantly (Figures 3a and b). Serum levels of alkaline phosphatase significantly decreased after treatment with denosumab ($P<0.01$, Figure 3c). Moreover, serum TRACP-5b persistently decreased during treatment with denosumab ($P<0.001$, Figure 3d). Of note, BMD continuously increased for 24 months (Figure 3e).

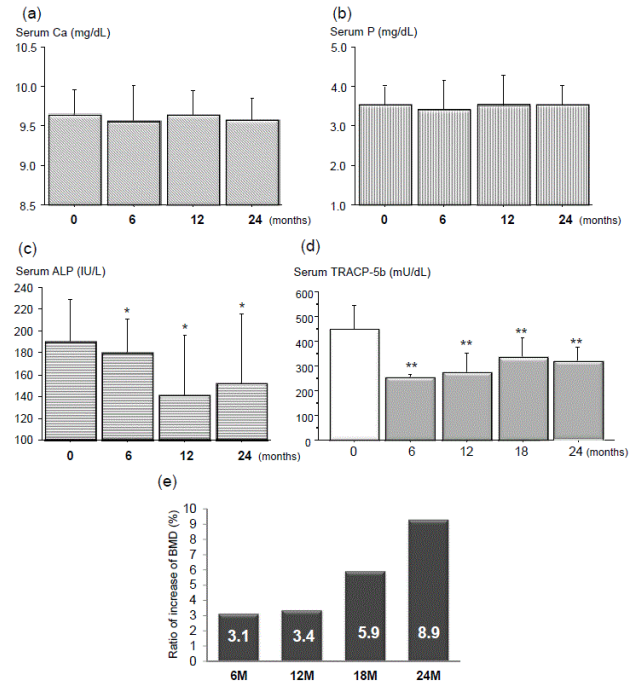

Figure 3: Changes of clinical markers during treatment with denosumab. a) Serum calcium and, b) phosphorus levels did not change significantly during course of denosumab treatment for 24 months. c) Serum levels of alkaline phosphatase significantly decreased after treatment with denosumab ($P<0.01$). d) Serum TRACP-5b persistently decreased during treatment with denosumab ($P<0.001$). e) Bone mineral density (BMD) persistently increased for 24 months.

Changes in serum calcium after injection of denosumab

The level of serum calcium was measured every 2 days after injection of denosumab. Serum calcium tended to decrease shortly after injection of denosumab (Figure 4). The decreases in serum calcium differed depending on the dose of vitamin D supplementation. A vitamin D dose of 0.5 to 1.0 μg/day was associated with maintenance of low serum calcium levels (Figure 4). The serum calcium of patients who were on hemodialysis

decreased more than that of other CKD patients. Importantly, levels of serum calcium in all patients recovered after 14 days, even though serum calcium decreased shortly after injection of denosumab.

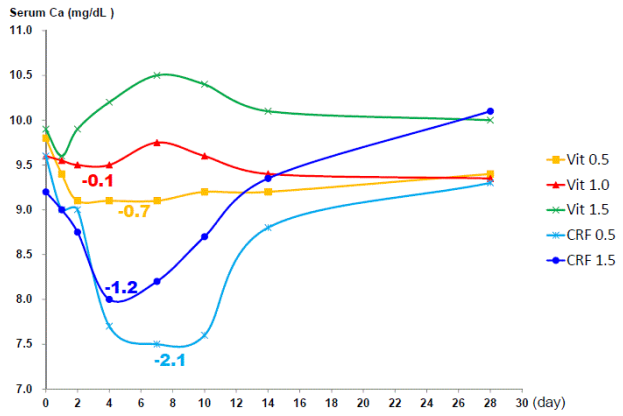

Figure 4: Changes of serum calcium levels shortly after injection of denosumab. Level of serum calcium was measured every 2 days after injection of denosumab. Serum calcium tended to decreased shortly after injection of denosumab. The results show that a dose of 0.5 to 1.0 μg/day vitamin D was appropriate to maintain serum calcium levels. Serum calcium decreased more in patients who were on hemodialysis than it did in other CKD patients. Though serum levels of calcium decreased shortly after injection of denosumab, those levels recovered within 14 days. Vit 0.5, supplementation with vitamin D 0.5 μg/day; Vit 1.0, supplementation with vitamin D 1.0 μg/day; Vit 1.5, supplementation with vitamin D 1.5 μg/day; CRF 0.5, supplementation with vitamin D 0.5 μg/day in hemodialysis patients; CRF 1.5, supplementation of vitamin D 1.5 μg/day in hemodialysis patients.

Discussion

Impaired renal function is a risk factor for osteoporosis, progressive bone loss, and ultimately, bone fractures. Several factors could explain the association between CKD and osteoporosis and osteopenia. Patients with CKD are likely to be older and have lower levels of vitamin D. In addition, there is increasing evidence that CKD itself is a risk factor for low BMD [4-7]. Patients with impaired renal function have been found to have greater rates of bone loss [7,20]. Nickolas et al. reported an independent correlation between an eGFR <60 mL/min/1.73 m^2 and the prevalence of hip fractures [21]. In addition, elevated serum cystatin C levels have been independently associated with risk for hip fracture [22,23].

Bisphosphonates are commonly prescribed to treat osteoporosis. However, several studies indicate that bisphosphonates are not efficacious for long-term improvement in BMD [10,11]. Moreover, several studies show poor medication adherence with bisphosphonates [24,25]. Nonadherence with oral bisphosphonates can be associated with significantly increased short-term risk of osteoporotic fractures. In fact, the present study clearly showed that more than half of patients with CKD treated with bisphosphonates had low BMD (<70% YAM) (Figure 1). In particular, patients treated with a corticosteroid for glomerulonephritis had low BMD despite bisphosphonate therapy. Importantly, BMD significantly increased in cases where the therapy was changed from bisphosphonates to denosumab (Figure 2). Denosumab is a potent antiresorptive with antifracture efficacy comparable to that of bisphosphonates. Bisphosphonates affect mature osteoclasts, whereas denosumab prevents osteoclast maturation, activation, and survival, thereby decreasing resorption of cortical and trabecular bone [15]. This may explain why denosumab appears to be more effective than bisphosphonates as a treatment for low BMD.

We also assessed the adverse effects of denosumab in patients with CKD. Although hypocalcemia was a concern, none of the participants showed symptomatic hypocalcemia (Figure 3a). Our results suggest that vitamin D supplementation is required to prevent hypocalcemia, and ideally should be initiated prior to treatment with denosumab because of the decrease of serum calcium that occurs shortly after the injection of denosumab (Figure 4). Higher amounts of vitamin D supplementation are required prior to use of denosumab for patients on hemodialysis. However, levels of serum calcium recovered within 14 days in each case. Moreover, vitamin D supplementation is important to elicit the effect of denosumab. A dose of 0.5 to 1.0 μg/day of vitamin D was required to elicit the effect of denosumab (data not shown). The frequent surveillance of serum and possibly urine calcium are demanded.

Irrespective of cause, patients with CKD have a greater prevalence of osteoporosis and are at increased risk for bone fractures. Despite this increased risk, the majority of studies evaluating osteoporosis therapy have attempted to exclude patients with CKD. The results of the present study suggest that denosumab is an effective intervention for osteoporosis management in patients with CKD. Impaired renal function does not affect the pharmacokinetics and pharmacodynamics of denosumab [26]. After administration of denosumab, serum levels of calcium decreased, as is expected with antiresorptive therapy. The serum calcium kinetics following administration of denosumab (Figure 4) provide evidence for the importance of adequate vitamin D supplementation in real-world clinical practice.

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