

# Safety and efficacy of denosumab in patients with multiple myeloma

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The safety and efficacy of denosumab were retrospectively assessed in patients with multiple myeloma. This study included 25 patients treated with denosumab from May 2012 to March 2014. No skeletal-related events (SREs) due to multiple myeloma occurred. Urine N-telopeptide/creatinine decreased in all of 5 assessed patients 1 month after denosumab treatment, and urine deoxypyridinoline/creatinine decreased in 4 of 5 assessed patients. Osteonecrosis of the jaw was not observed. Hypocalcemia developed in 11 patients (44%). One patient with Grade 4 hypocalcemia complained of numbness of the extremities; however, the other patients had no complaint. On univariate analysis, the incidence of hypocalcemia was significantly higher in patients with than in those without renal insufficiency ( $p = 0.007$ ) and patients with high than in those with low  $\beta$ -2-microglobulin ( $p = 0.017$ ). On multivariate analysis, renal insufficiency was a risk factor for the development of hypocalcemia ( $p = 0.01$ ). The patients who had prophylactic Ca and vitamin D<sub>3</sub> supplementation had a significantly lower incidence of hypocalcemia than the others ( $p = 0.047$ ). In conclusion, treatment with denosumab is safe and effective to prevent SREs in patients with multiple myeloma. Prophylaxis for hypocalcemia with calcium and/or vitamin D<sub>3</sub> supplementation is necessary, especially in patients with renal insufficiency.

Key words: multiple myeloma, denosumab, RANK ligand, hypocalcemia

## Introduction

Bone disease is one of the clinical features of multiple myeloma and has a significant negative impact on both survival and quality of life in patients with multiple myeloma. Bone disease of myeloma is the result of signals that promote bone resorption and inhibit bone formation. In particular, osteoclastic activity is magnified by cell to cell signals mediated by RANK (receptor activator of NF-kappa B)/RANKL (RANK ligand) and negatively regulated by osteoprotegerin<sup>1-6</sup>. Despite the availability of bisphosphonates such as zoledronic acid for the treatment of multiple myeloma bone disease, an unmet medical need exists for a more convenient, effective, and safe therapy. Parenteral bisphosphonates must be administered by intravenous infusion, and they are not effective

in all patients. Renal toxicity may limit the dose and use of these agents in myeloma patients with renal dysfunction<sup>7</sup>. Denosumab is a fully monoclonal antibody to RANKL that has high affinity and specificity for RANKL, and it has been reported to be effective in patients with bone disease induced by many malignancies, including multiple myeloma<sup>8,9</sup>. The safety and efficacy of denosumab were retrospectively assessed in Japanese patients with multiple myeloma.

## Patients and Methods

This study included 25 myeloma patients treated with denosumab for their bone disease from May 2012 to March 2014 in order to evaluate the safety and efficacy of denosumab. The diagnosis of multiple myeloma was made according to the criteria of the International Myeloma Working Group<sup>10</sup>.

Patients received subcutaneous denosumab 120 mg every 4 weeks. Since the launch on April 2012, denosumab has been administered to about 7,300 patients as of August 2012, and 32 cases of serious hypocalcemia, including 2 deaths, have been reported in Japan. The Ministry of Health, Labour and Welfare (MHLW)/ Pharmaceuticals and Medical Devices Agency (PMDA) instructed the Daiichi-Sankyo CO., LTD to distribute the Dear Healthcare Professional Letter of Rapid Safety Communication ("Blue Letter") on September 2012 (<https://www.pmda.go.jp/files/000148439.pdf>). This letter highly rec-

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ommends supplemental calcium and vitamin D administration for all patients unless the serum calcium level is high. According to this recommendation, 12 patients diagnosed after September 2012 received prophylaxis of calcium and vitamin D<sub>3</sub>. The following data were collected from medical records: SREs, physical examinations, performance status, vital signs, concomitant medications, hematology, and serum chemistry. In 5 patients, bone turnover markers, including urine N-telopeptide/creatinine (uNTx/uCr), urine deoxypyridinoline/creatinine (uDPD/uCr), serum bone-specific ALP (BSAP), osteocalcin (OC), and serum albumin-adjusted calcium, were assessed at the time of initiation of denosumab and 1 month after the start of therapy. Adverse events were evaluated according to CTCAE version 5.

Univariate and multivariate analyses of the risk factors for hypocalcemia were performed using Fisher's exact test and logistic regression analysis.

## Results

### Patient characteristics

The characteristics of the 25 patients are shown in Table 1; 16 (64%) were newly-diagnosed patients, and 9 (36%) were relapsed patients. The median age was 65 years (range 46–85 years), and the male/female ratio was 0.67 (10/15). The

**Table 1.** Patient characteristics n = 25

newly-diagnosed/ relapsed patients	16/9 (64%/36%)
Median age (range), years	65 (46–85)
Male	10 (40%)
PS (0:1:2:3:4)	9:11:2:3:0
Immunoglobulin subtype	
IgG	14 (56%)
IgA	7 (28%)
Light chain only	4 (16%)
Durie & Salmon stage at diagnosis	
I	4 (16%)
II	4 (16%)
III	17 (47%)
ISS stage at diagnosis	
1	6 (24%)
2	9 (36%)
3	10 (40%)
Bone scale >1	23 (92%)
Anemia (Hb <10 g/dL)	18 (72%)
Renal dysfunction (CCr <60)	8 (32%)
Beta-2-microglobulin >3.5	9 (36%)
Previous bisphosphonate treatment	15 (60%)
Anti-myeloma therapy	
Bortezomib-based regimen	11 (44%)
Lenalidomide-based regimen	10 (40%)
Thalidomide-based regimen	1 (4%)
None	3 (12%)

immunoglobulin subtypes were: IgG, 14 patients (56%); IgA, 7 patients (28%); and light chain only, 4 patients (16%). Performance statuses were: 0, 9 patients; 1, 11 patients; 2, 2 patients; and 3, 3 patients. Clinical stages stratified by the Durie & Salmon staging system at diagnosis were: stage I, 4 patients (16%); II, 4 patients (16%); and III, 17 patients (47%). ISS stages were: 1, 6 patients (24%); 2, 9 patients (36%); and 3, 10 patients (40%). There were 23 (92%) patients with a bone scale score over 2. The numbers of patients with anemia (Hb <10 g/dL), renal dysfunction (creatinine clearance <60 mL/min), and high beta-2-microglobulin (>3.5 mg/L) were 18 (72%), 8 (32%), and 9 (36%), respectively. The number of patients previously treated with bisphosphonate was 15 (60%).

The duration of treatment with denosumab was 3–22 months (median 12 months). The anti-myeloma therapies that were administered with denosumab were a bortezomib-based regimen (11 patients, 44%), a lenalidomide-based regimen (10 patients, 40%), and a thalidomide-based regimen (1 patient, 4%), respectively. Three patients (12%) received no anti-myeloma therapy.

### Efficacy

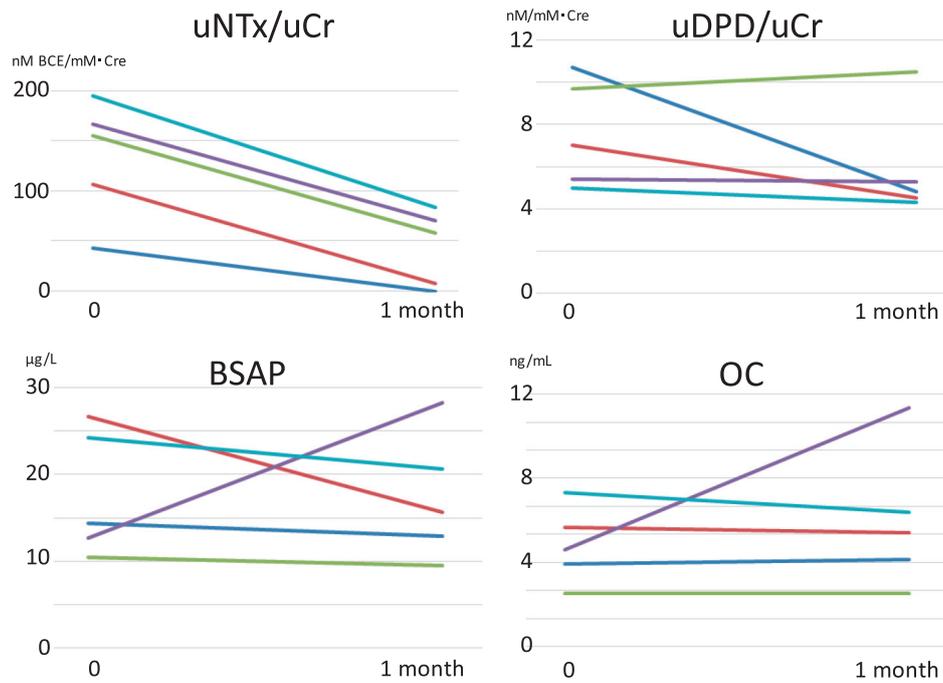
No SREs due to multiple myeloma occurred. Denosumab was discontinued in 5 patients because of disease progression or death (3 patients), patient's preference (1 patient), and an adverse event (hypocalcemia, 1 patient).

Of the bone resorption markers, uNTx/uCr decreased in 5 patients 1 month after denosumab treatment, uDPD/uCr and BSAP decreased in 4 patients, and OC decreased in 3 patients (Fig. 1).

### Adverse events

Osteonecrosis of the jaw due to denosumab was not observed in this study. Hypocalcemia developed in 11 patients (44%). Grades 1, 2, 3, and 4 hypocalcemia were observed in 8 patients, 2 patients, 0 patients, and 1 patient, respectively. The patient with Grade 4 hypocalcemia was only one who had severe renal impairment (creatinine clearance <30 mL/min), and complained of numbness of the extremities; however, the other patients had no complaints.

On univariate analysis, the incidence of hypocalcemia was significantly higher in patients with than in those without renal insufficiency ( $p = 0.007$ ) and patients with high than in those with low  $\beta$ -2-microglobulin ( $p = 0.017$ ). On multivariate analysis, renal insufficiency was the only risk factor for the development of hypocalcemia ( $p = 0.01$ ). The patients who had prophylactic Ca and vitamin D<sub>3</sub> supplementation had a significantly lower incidence of hypocalcemia than the others ( $p = 0.047$ ) (Table 2). In patients with normal creatinine clearance ( $\geq 60$  mL/min), 2 of 6 patients (33.3%), who did not



**Figure 1.** Bone turnover markers, including urine N-telopeptide/creatinine (uNTx/uCr), urine deoxypyridinoline/creatinine (uDPD/uCr), serum bone-specific ALP (BSAP), and osteocalcin (OC).

**Table 2.** Risk factors of hypocalcemia

		hypocalcemia		Univariate analysis	Multivariate analysis
		-	+	p value	
Age	<65	7	5	NS	NS
	≥65	7	6		
Gender	male	6	4	NS	NS
	female	8	7		
Previous bisphosphonate treatment	-	8	7	NS	NS
	+	6	4		
Prophylaxis with Ca/Vitamine D3	-	4	8	0.047	NS
	+	10	3		
Creatinine clearance	<60	1	7	0.007	p = 0.01
	≥60	13	4		
Hb	<10 g/dL	12	6	NS	NS
	≥10 g/dL	2	5		
Beta-2-microglobulin	<3.5	12	4	0.017	NS
	≥3.5	2	7		

NS: not significant

received prophylactic Ca and vitamin D3 supplementation, showed hypocalcemia, but only 2 of 11 patients (18.2%), who received prophylaxis, showed hypocalcemia. Four patients showed hypocalcemia within one week, and the median time to hypocalcemia was 14 days.

In this study, there were no other serious adverse events due to denosumab, including anaphylaxis and skin infection.

### Discussion

Denosumab (Ranmark®, Daiichi Sankyo Co., LTD, Tokyo, Japan) was approved as a drug for the treatment of bone disease in myeloma patients in April 2014 in Japan, the only country in the world; thus, it is very important to assess its efficacy and safety in myeloma patients.

In this study, no SREs were observed. Fizazi et al. reported

that the incidence of SREs was 8% over a 25-week treatment period with denosumab<sup>11)</sup>. In the present study, uNTx and uDPD, which are bone resorption markers, decreased markedly 1 month after denosumab treatment. According to these data, denosumab might be effective to prevent SREs in patients with multiple myeloma; however, long-term observation is necessary for an accurate evaluation.

The present data showed that hypocalcemia occurred between 1 week and 2 months after the initiation of denosumab treatment. In 4 cases, hypocalcemia occurred within 1 week. It has been reported that single subcutaneous doses of denosumab of 1.0 and 3.0 mg/kg demonstrated non-linear pharmacokinetics, with a maximum serum concentration between 7 and 14 day<sup>12,13)</sup>. According to these reports, it is suspected that hypocalcemia will occur within 14 days because of the maximum serum concentration of denosumab; thus, careful observation is necessary 2 weeks after the initiation of denosumab treatment.

Block et al. evaluated pharmacokinetics and pharmacodynamics of denosumab in patients with renal function ranging from normal to severe renal failure requiring dialysis, and they discussed that this drug might be less nephrotoxic than bisphosphonate in patients with renal impairment<sup>14)</sup>. In the present study, renal function did not deteriorate with denosumab; however, the frequency of hypocalcemia was significantly higher in myeloma patients with renal insufficiency during denosumab treatment, especially with severe renal impairment (creatinine clearance <30 mL/min). Okada et al. assessed the frequency of hypocalcemia in 53 patients treated with denosumab and reported that non-administration of zoledronic acid and creatinine clearance less than 50.0 mL/min were independent risk factors for denosumab-induced hypocalcemia<sup>15)</sup>. According to this report and the present study, careful observation of serum Ca levels is necessary in myeloma patients with renal insufficiency. The present study showed that calcium and/or vitamin D<sub>3</sub> supplementation is useful to prevent hypocalcemia in patients with normal renal function like patients with renal insufficiency, as previously reported<sup>16)</sup>.

In conclusion, treatment with denosumab is safe and effective to prevent SREs in Japanese patients with multiple myeloma. Prophylaxis for hypocalcemia with calcium and/or vitamin D<sub>3</sub> supplementation is necessary, especially in patients with renal insufficiency.

### Conflict of Interest

The authors declare no conflict of interest.

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