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ORIGINAL ARTICLE

Eldecalcitol increases bone mineral density in Chinese osteoporotic patients without vitamin D or calcium supplementation

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Abstract
Eldecalcitol increased bone mineral density (BMD) and prevented vertebral fractures in vitamin D-sufficient osteoporotic subjects. However, the effect of eldecalcitol on BMD under vitamin D insufficiency is unknown. We examined the effect of eldecalcitol on BMD compared with alfacalcidol in osteoporotic patients without vitamin D or calcium supplementation. This is a randomized, double-blind, active comparator trial. 265 Chinese osteoporotic patients were randomly assigned to receive 0.75 μg eldecalcitol or 1.0 μg alfacalcidol for 12 months without vitamin D or calcium supplementation. Baseline calcium intakes were less than 550 mg/day and mean serum 25-hydroxyvitamin D [25(OH)D] was below 43 nmol/L in both groups. Baseline BMD tended to be lower in patients with lower calcium intake and serum 25(OH)D. Lumbar BMD increased by 2.05% higher in eldecalcitol than alfacalcidol group at 12 months. Total hip and femoral neck BMD also increased by 1.33 and 1.78%, respectively, in the eldecalcitol than the alfacalcidol group. The effect of eldecalcitol on BMD was not affected by serum 25(OH)D or calcium intake. The incidence of adverse events was not different between the two groups. Incidence of hypercalcemia in the edecalcitol group was not affected by serum 25(OH)D. In conclusion, baseline BMD tended to be lower in patients with low calcium intake and serum 25(OH)D. Eldecalcitol increased lumbar and hip BMD more than alfacalcidol regardless of serum 25(OH)D or calcium intake without vitamin D or calcium supplementation. These results suggest that eldecalcitol is effective in increasing the BMD of osteoporotic patients regardless of vitamin D status or calcium intake.
Clinical Trial Registration number JAPIC CTI 152904.

Keywords Eldecalcitol · Osteoporosis · Bone mineral density · Vitamin D · Calcium

Introduction

Low calcium intake and vitamin D insufficiency are known risk factors for osteoporosis. The FAO/WHO recommends a calcium intake of 1000–1300 mg/day for adults [1]. At present there is no worldwide consensus on the optimum levels of serum 25-hydroxyvitamin D[25(OH)D]; however, the International Osteoporosis Foundation Working Group has discussed target levels of 50–75 nmol/L of serum 25(OH)D [2], and the Institute of Medicine and the Endocrine Society

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are in disagreement as to whether the cutoff for vitamin D deficiency should be defined as a serum 25(OH)D level of 50 nmol/L or a higher level [3–6]. In light of these values, the IOF published results of a systematic review which showed very low calcium intakes and suboptimal vitamin D status in Asia–Pacific countries [7, 8]. The mean levels of calcium intake and serum 25(OH)D reported in China are also very low, at 403 mg/day for calcium [9] and 49.7 nmol/L for serum 25(OH)D [10]. Along with the low calcium intake and low serum 25(OH)D level, the changes in lifestyle with urbanization and aging have increased hip fractures in Beijing, China [11].

In most clinical trials of anti-osteoporotic drugs, patients receive native vitamin D and calcium supplementation [12–28], because a sufficient level of serum 25(OH)D is required for the anti-osteoporosis drugs to work. Alendronate showed lower BMD increase in patients whose baseline 25(OH)D concentration was below 62.5 nmol/L than in patients with a serum 25(OH)D concentration of above 62.5 nmol/L at baseline [29, 30]. However, the effects of active vitamin D compounds on bone and calcium metabolism may develop regardless of the serum 25(OH)D level.

Eldecalcitol is an analog of 1α, 25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), bearing a hydroxypropyloxy residue at the 2β position. A phase 2 clinical study examined the effect of eldecalcitol treatment for 12 month on lumbar and hip BMD in Japanese patients with osteoporosis [31]. To rule out the possibility that the effect of eldecalcitol on BMD may merely be a supplementary effect of eldecalcitol on vitamin D deficiency, the patients were supplemented with 400 IU/day vitamin D_3 when serum 25(OH)D was below 50 nmol/L, and with 200 IU/day vitamin D_3 when serum 25(OH)D was at or higher than 50 nmol/L. As a result, serum 25(OH)D was at or higher than 50 nmol/L in more than 92% of the participants. After 12 months of treatment with 0.75 μg eldecalcitol, increase in lumbar and total hip BMD was higher compared to those in the placebo group by 3.3% and 1.5%, respectively [32]. Later subgroup analysis revealed that the effects of eldecalcitol on the lumbar spine and total hip BMD after 12 months of treatment were not different between patients in the lower tertile (< 62.5 nmol/L when measured at 3 months) and in the upper tertile (> 72.5 nmol/L at 3 months) of serum 25(OH)D [33]. Subsequent 3-year, randomized, double-blind clinical trial comparing the effects of eldecalcitol with those of alfacalcidol on fracture and BMD demonstrated that eldecalcitol significantly increased lumbar and total hip BMD and reduced incident vertebral fractures [31]. Those studies demonstrated that eldecalcitol increases lumbar and hip BMD and prevents vertebral fractures under vitamin D sufficiency state. However, it has been unclear whether eldecalcitol is also effective in increasing vertebral and hip BMD under vitamin D deficiency.

The present study was undertaken to examine the effect of eldecalcitol on BMD in Chinese osteoporotic patients with low nutritional vitamin D and calcium intake. The patients were not supplemented with vitamin D_3 or calcium throughout the study, and most of them were under vitamin D deficiency/insufficiency state with low calcium intake. The results demonstrate that eldecalcitol treatment for 12 months can increase lumbar spine, total hip, and femoral neck BMD more than alfacalcidol to similar levels to those in the previous studies [31, 32] in Chinese osteoporotic patients without vitamin D or calcium supplementation.

Materials and methods

Study design

This is a randomized, active comparator, double blind double dummy multicenter study to compare the efficacy of eldecalcitol with alfacalcidol in Chinese osteoporotic patients. The study was approved by the State Food and Drug Administration of China (2014L02213) and conducted at endocrinology, orthopedics or bone metabolism disease department in hospitals which were qualified as clinical trial center by the State Food and Drug Administration of China. The protocol was approved by the ethics committee at each center, and informed consent was obtained from each patient. Chinese patients were randomly assigned to receive either 0.75 μg eldecalcitol (Chugai Pharmaceutical Co., Ltd.) and alfacalcidol placebo or 1.0 μg alfacalcidol and eldecalcitol placebo once a day for 12 months. Randomization was performed by a computerized system. Patients received no vitamin D or calcium supplementation during this study. Compliance with the study treatment was assessed with the use of medication diaries and counts of remaining medication supplies.

Patients

Patients were enrolled if their lumbar spine (L1–4) BMD T-score was below − 2.5 SD of the Chinese reference values provided by the manufacturer of the bone densitometer. Patients with lumbar spine (L1–4) BMD T-score between − 1.0 and − 2.5 SD were enrolled if they had fragility fractures in the vertebrae, hip, humerus, or forearm. Female patients were at least 3 years after menopause or more than 60 years of age. Patients were excluded if they had any severe bone disorder or deformation at the lumbar spine that would affect dual-energy X-ray absorptiometry (DXA) measurement; had any disorders such as primary hyperparathyroidism, Cushing's syndrome, hyperthyroidism, gonadal insufficiency, poorly controlled diabetes mellitus (HbA1c over 9%), or other causes of secondary osteoporosis; or had a history of urolithiasis at any time. Patients were also

excluded if they had taken any oral bisphosphonates, either within the 2 months before entry or for more than 4 weeks during the 12 months before entry; had taken glucocorticoids, calcitonin, vitamin K, active vitamin D compounds, selective estrogen receptor modulators, hormone replacement therapy, or Chinese medicine for osteoporosis treatment within the past2 months; had received intravenous bisphosphonates, parathyroid hormone, anti-RANKL antibody, or cathepsin K inhibitor, at any time; had serum calcium levels above 10.4 mg/dL or a urinary calcium excretion of over 400 mg/gCr; had serum creatinine levels above the reference range; had any clinically significant hepatic or cardiac disorder; had a history of malignant tumor.

Treatment was discontinued if serum calcium became > 11.0 mg/dL (2.74 mmol/L). If serum calcium did not become > 11 mg/dL but became > 10.4 mg/dL (2.59 mmol/L) in two consecutive measurements or the urinary calcium excretion became > 400 mg/gCr in two consecutive measurements, and if the investigator judged that serum or urinary calcium increase was progressive, treatment was discontinued.

End points

The primary end point was change in BMD in the lumbar spine. Secondary end points were change in BMD in the total hip and femoral neck; changes in bone turnover markers, including bone-specific alkaline phosphatase (BALP) as bone formation markers and serum type I collagen C-telopeptide (CTX) as bone resorption markers. Other end points included incidence of new vertebral fractures and any non-vertebral fractures. All investigators who performed end point evaluations were unaware of the study-group assignments of the patients.

Measurements

DXA of the lumbar spine in the posterior anterior projection and the total hip was performed at baseline and at 6 and 12 months, using a Hologic (Discovery) or Lunar (DPX, iDXA, Prodigy) bone densitometer. A central facility (Bioclinica, Portland, OR, USA) performed quality assurance of the longitudinal adjustment and analysis of the BMD measurements. To account for differences in the DXA machines, each machine was calibrated with standardized phantoms.

Serum and spot urine samples were collected at baseline and at 1, 3, 6, and 12 months for routine chemical analyses, including serum and urinary calcium, hematologic indices, and markers of hepatic and renal function. At baseline and at 3, 6, and 12 months, we determined the following bone turnover markers: serum BALP (MicroVue BAP EIA; Quidel Corp., San Diego, CA, USA), serum CTX (Elecsys beta-CrossLaps kit; Roche Diagnostics). Also at baseline and at 3, 6, and 12 months, we determined serum intact PTH (measured at each sites), 25(OH)D (LIAISON 25 OH Vitamin D TOTAL Assay; DiaSorin Inc.), and $1,25(OH)_2D_3$ (LCMS/MS assay). Serum calcium is corrected with the following formula if serum albumin is less than 4.0 g/dL: Corrected serum calcium (mg/dL) = serum calcium + (4.0 − serum albumin).

Lateral radiographs of the thoracic and lumbar spine were taken at baseline, and at 6 and 12 months or at termination. Vertebrae from T4 to L4 were evaluated independently by two expert investigators. Prevalent fractures and any incidence of a new vertebral fracture were diagnosed by the semi-quantitative method [34]. If discrepant results were obtained by the two investigators, the final assessment was made by both investigators conferring on the discrepancy. All the radiologic specifications and the levels of vertebra to be included in the examination of the thoracic and lumbar spine were standardized throughout the study sites. Non-vertebral fractures were reported by the study investigators.

Dietary calcium intake was calculated based on a 3-day diet survey before the first dosing. The calcium content of each food was determined from values published in the *Chinese Food Composition List*, Book1, Second edition [35]. If a particular food was not listed in that publication, then we also referred to *Chinese Food Composition List*, Book2, 2004 edition [36].

Adverse events

All patients were questioned about adverse events of treatment at each visit, and all adverse events reported during 1 month of follow-up were analyzed regardless of the investigators' assessments of causality. The Medical Dictionary for Regulatory Activities (MedDRA, Version 18.1) was used to categorize reported adverse events. We report all categories of adverse events for which the frequency was at least 5%.

Statistical analysis

All randomized patients who had taken at least one dose of the study drug were included for safety analysis, and all randomized patients with drug administration who had both a baseline assessment and at least one post-randomization assessment were included in the full analysis set (Table 1).

The difference between treatment groups (together with the 95% confidence interval) in the percentage change in L1–L4 BMD from baseline to 12 months was calculated using a mixed-effects model repeated measures (MMRM) approach with unstructured covariance matrices including as fixed effects the baseline L1–L4 BMD, treatment group, visit, and interactions of group and visit (two-sided test at significance level $\alpha = 0.05$). Statistical analyses including subgroup analyses were pre-specified in statistical analysis

Table 1 Patient disposition and baseline characteristics of patients in the full analysis sets

Patient disposition	Eldecalcitol	Alfacalcidol
Randomized	137	128
Treated	136	127
Completed 12 months	122	101
Discontinued study	14	26
Withdrew consent	10	12
Adverse event other than calcium increase	2	6
Adverse events of calcium increase	1	1
Reasons other than adverse events	1	7
Safety set	136	127
Full analysis set	128	121
Baseline characteristics of patients in the full analysis sets	Eldecalcitol, $n=128$	Alfacalcidol, $n=121$
Age (years)	66.0 ± 6.9	64.9 ± 7.1
Male patients	2 (1.6%)	5 (4.1%)
Height (cm)	155.3 ± 5.3	155.5 ± 5.5
Body-mass index (kg/m^2)	22.6 ± 3.5	22.7 ± 3.0
Lumbar spine L1–L4 BMD T-score	−2.86 ± 0.71	−2.84 ± 0.61
Total hip BMD T-score	−1.95 ± 0.72	−1.91 ± 0.70
Femoral neck BMD T-score	−2.30 ± 0.74	− 2.24 ± 0.75
Serum BALP (U/L)	44.1 ± 10.7	42.3 ± 10.4
Serum CTX (nmol BCE/mmol Cr)	0.56 ± 0.24	0.54 ± 0.20
No. of prevalent vertebral fractures		
0	91 (71.1%)	78 (64.5%)
1	27 (21.1%)	26 (21.5%)
≥ 2	10 (7.8%)	17 (14.0%)
Ca intake (mg/day)	500 ± 268	549 ± 271
Corrected serum Ca (mg/dL)	9.31 ± 0.36	9.32 ± 0.40
Urinary Ca excretion (mg/gCr)	137 ± 82	145 ± 79
Serum creatinine (mg/dL)	0.69 ± 0.12	0.69 ± 0.14
Serum 25(OH)D (nmol/L)	38.9 ± 15.7	42.5 ± 20.8

Data are means ± SD for the indicated number of patients in each group or number (%)

If there are several reasons for discontinuation, the main reason reported by the investigator is listed

The number of patients for whom we measured total hip *T*-score and femoral neck *T*-score are 127 in the eldecalcitol group and 120 in the alfacalcidol group

The number of patients for whom we measured serum BALP and serum CTX is 127 in the eldecalcitol group and 121 in the alfacalcidol group

The number of patients for whom we measured serum creatinine and 25(OH)D is 136 in the eldecalcitol group and 127 in the alfacalcidol group

plan before opening the randomization code. The subgroup analyses by the tertile of 25(OH)D and calcium intake in eldecalcitol group were conducted as ad hoc analyses.

The study had a power of 90% (with a two-sided alpha of 0.05) to detect a 2.3 ± 4% (mean ± SD) difference of percentage change in L1–L4 BMD from baseline to 12 months between both groups, assuming a percentage change in L1–L4 BMD of 2.9% and 0.6% in the eldecalcitol and alfacalcidol groups, respectively, with 65 patients. However, to evaluate the safety in Chinese primary osteoporosis patients, at least 100 subjects per arm is required for registration study in China. We planned to enroll 120 patients per arm assuming an estimated 20% discontinuation rate.

The data and assessments collected in this study were held by EPS International, a contract research organization (CRO), and statistical analyses were performed by EPS International. Data concerning BMD, bone turnover markers, intact PTH, 25(OH)D, and 1,25$(OH)_2D_3$, and the evaluations of spinal radiographs were analyzed centrally by independent investigators and then transferred to EPS International for statistical analysis. The authors had access to all the data and take responsibility for the veracity of the analysis.

Results

Baseline characteristics of the patients

This study included 265 Chinese patients from 16 centers in China and 249 subjects (242 women and 7men, aged from 48 to 83 years) were included in the full analysis set (Table 1). There were no differences in baseline characteristics between the alfacalcidol- and eldecalcitol-treated groups (Table 1). The mean daily calcium intake was less than 550 mg/day in both the eldecalcitol and alfacalcidol groups, which is far less than the recommended amount of 1000–1300 mg/day [1]. Mean serum 25(OH)D levels were below 50 nmol/L in both the eldecalcitol and alfacalcidol groups at baseline. Serum 25(OH)D levels were almost constant throughout the study period and were 38.1 ± 15.2 and 40.5 ± 16.6 nmol/L (mean ± SD) in the eldecalcitol and alfacalcidol groups, respectively, at the end of the study.

When patients were divided by tertiles of baseline serum 25(OH)D (upper tertile ≥ 45.0 nmol/L, lower tertile < 30.0 nmol/L) and tertiles of calcium intake (upper tertile ≥ 595 mg/day, lower tertile < 371 mg/day), there was a tendency for lumbar spine, total hip and femoral neck BMD to be lower in the lower tertile of serum 25(OH)D, and was lowest in the lower tertiles of both serum 25(OH)D and calcium intake (Fig. 1a). Baseline urinary calcium tended to be lower in the lower tertile of calcium intake, but did not appear to be influenced by serum 25(OH)D (Fig. 1b). There was also a tendency that baseline serum calcium was lower and intact PTH was higher in the lower tertile of serum 25(OH)D or calcium intake (Fig. 1b).

BMD of lumbar spine, total hip, and femoral neck

BMD of the lumbar spine increased within 6 months of eldecalcitol treatment and gradually increased thereafter until 12 months (Fig. 2a). After 12 months of eldecalcitol treatment, lumbar spine BMD, as a primary end point, had

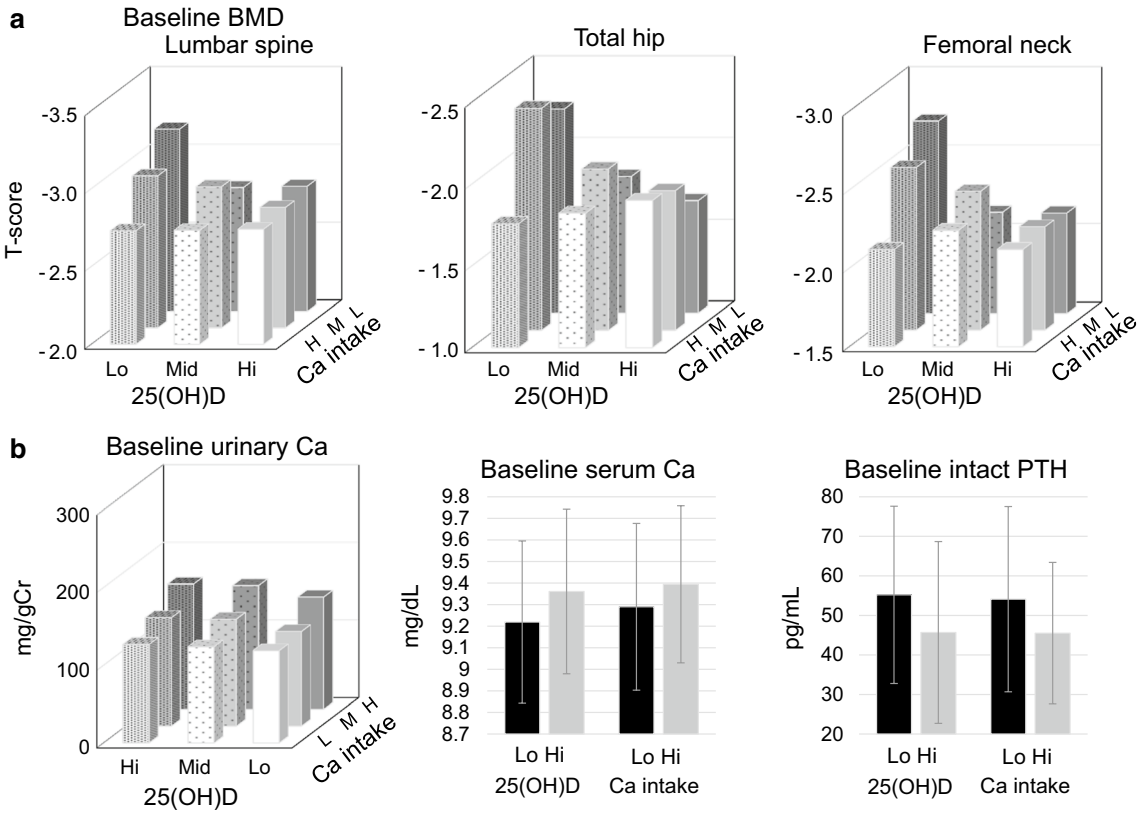

Fig. 1 **a** Baseline bone mineral density (BMD) in the lumbar spine (L1–L4), total hip, and femoral neck relative to baseline serum 25(OH)D and dietary calcium intake in the eldecalcitol group. Data are means. BMD was not adjusted by any other factors. **b** Baseline urinary calcium excretion relative to baseline serum 25(OH)D and dietary calcium intake, and baseline serum calcium and intact PTH relative to baseline serum 25(OH)D or dietary calcium intake in the eldecalcitol group. 25(OH)D level: lower tertile < 30.0 nmol/L, upper tertile ≥ 45.0 nmol/L; dietary calcium intake: lower tertile < 371 mg/day, upper tertile ≥ 595 mg/day. Higher *Y* axis showed lower BMD in the three dimensional bar charts. The order of Hi and Lo in the three-dimensional bar charts are opposite between **a** and **b**. Data are means ± SD

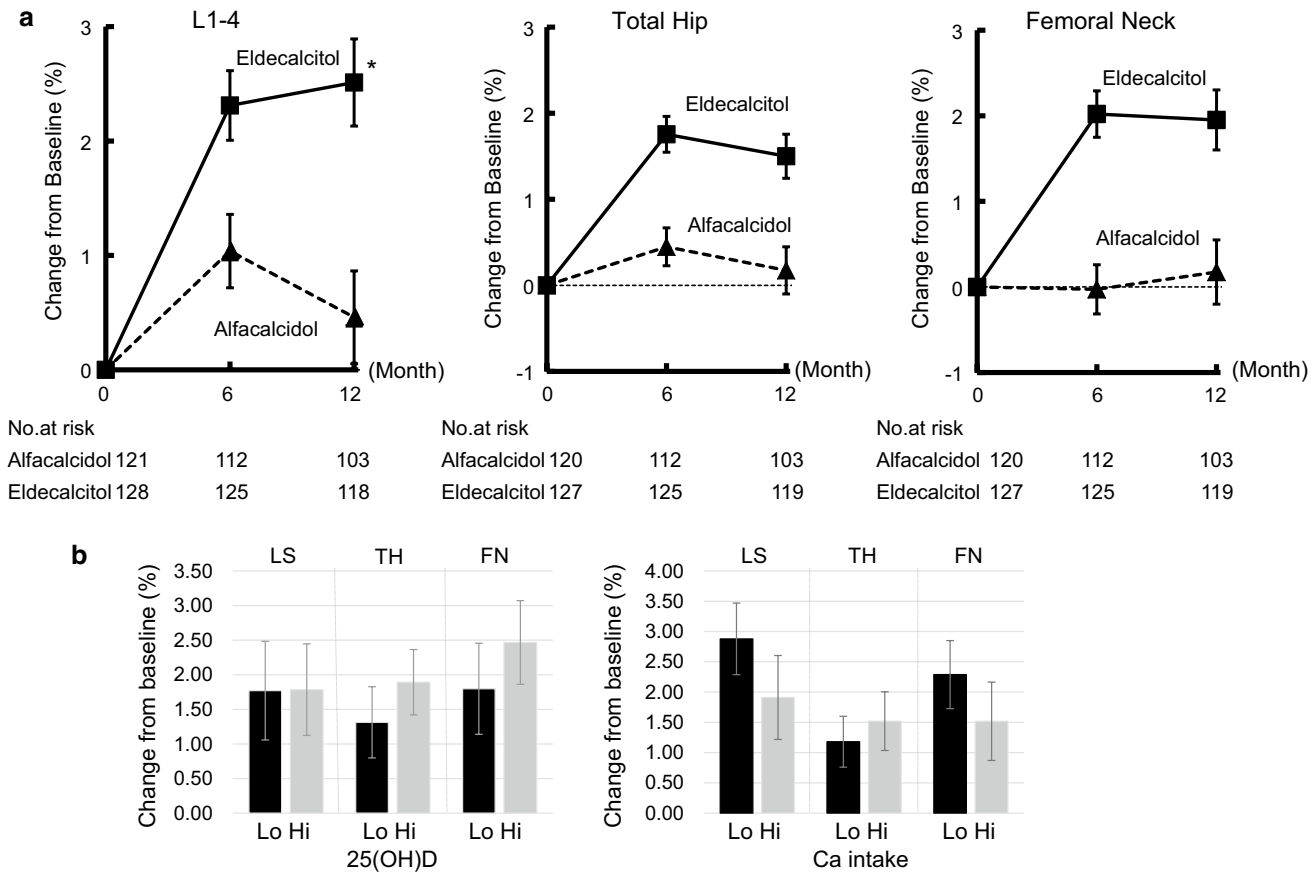

Fig. 2 **a** Changes in bone mineral density (BMD) in the lumbar spine (L1–L4), total hip, and femoral neck during the study period. **b** Change in BMD at 12 months in the lumbar spine (LS), total hip (TH), and femoral neck (FN) relative to baseline serum 25(OH)D or dietary calcium intake in eldecalcitol group. 25(OH)D level: lower tertile < 30.0 nmol/L, upper tertile ≥ 45.0 nmol/L; dietary calcium intake: lower tertile < 371 mg/day, upper tertile ≥ 595 mg/day. Data are LS means ± SE. *$p < 0.001$

increased from baseline by 2.51%, whereas the increase in lumbar spine BMD was only 0.46% in the alfacalcidol group [least square (LS) mean difference, 2.05%; 95% confidence interval (CI) 0.96–3.15; $p < 0.001$]. Total hip and femoral neck BMD had increased by 1.50% and 1.95%, respectively, at 12 months in the eldecalcitol group (Figs. 2a). In contrast, total hip and femoral neck BMD remained almost constant and increased by only 0.17% in both sites after 12 months of alfacalcidol treatment. As a result, there was a difference in total hip and femoral neck BMD between the eldecalcitol and alfacalcidol groups at 12 months (1.33% and 1.78%, 95% CI 0.59–2.07 and 0.76–2.79, respectively).

The effect of eldecalcitol on BMD at any site was not different between patients in the upper and lower tertiles of serum 25(OH)D or calcium intake(Figs. 2b).

Bone turnover markers

As a bone formation marker, mean serum BALP decreased from baseline by 39% at 12 months in the eldecalcitol group. Alfacalcidol treatment suppressed serum BALP by 23% at 12 months, which was less than the effect of eldecalcitol (LS mean difference, − 15.4%; 95% CI − 20.3 to − 10.6) (Fig. 3a). The patients were stratified into tertiles according to baseline levels of serum BALP. Because eldecalcitol suppressed BALP more strongly in the upper tertiles than in the lower tertiles of serum BALP, the median value of serum BALP in all subgroups of eldecalcitol-treated subjects decreased to within or close to the reference range. In the alfacalcidol group, the median value of serum BALP in the upper and mid tertiles of patients did not fall within the reference range throughout the treatment period (Fig. 3a).

As a bone resorption marker, median serum CTX decreased from baseline by 24% after 12 months of eldecalcitol treatment and remained suppressed throughout the study period. Alfacalcidol treatment did not suppress serum CTX (LS mean difference, − 38.5%; 95% CI − 50.0 to − 27.1) (Fig. 3b). Again, because eldecalcitol suppressed serum CTX more strongly in subjects with upper tertile than in lower tertile of serum CTX, it decreased to the reference

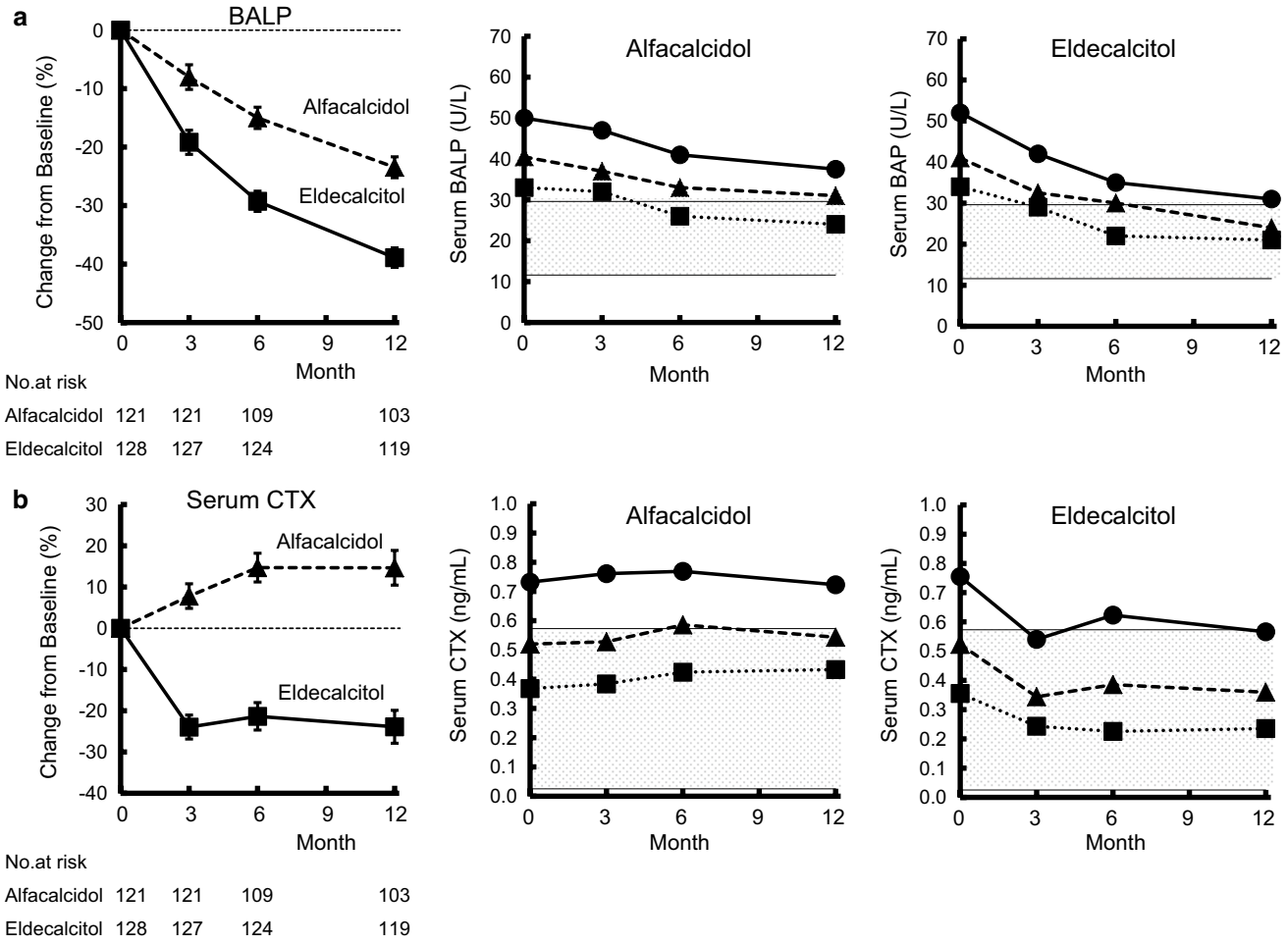

Fig. 3 Changes in **a** serum bone-specific alkaline phosphatase (BALP; a bone formation marker) and **b** serum type I collagen C-telopeptide (CTX; a bone resorption marker) during the study period. Data are means ± SE. Change in serum BALP and serum CTX relative to baseline level during 12 months. Levels of serum BALP and serum CTX in each tertile are shown separately for each treatment. Serum BALP: reference range, 11.6–29.6 U/L; serum CTX: reference range, 0.025–0.573 ng/mL. The reference ranges were cited from the analysis kit manufacturers' manuals. The reference samples were taken from healthy premenopausal women. Closed squares, low level (tertile 1, serum BALP < 38.0 U/L, serum CTX < 0.435 ng/mL); closed triangles, medium level (tertile 2, serum BALP ≥ 38.0 U/L, < 46.0 U/L, serum CTX ≥ 0.435 ng/mL, < 0.631 ng/mL); and closed circles high level (tertile 3, serum BALP ≥ 46.0 U/L, serum CTX ≥ 0.631 ng/mL). Data are median values

range in all tertiles of patients after 12 months. In the alfacalcidol group, median serum CTX in the upper tertile of patients did not fall within the reference range throughout the treatment period (Fig. 3b). These results are similar to those in the previous report, showing that eldecalcitol does not suppress bone turnover below the normal level [37].

Calcium-regulating hormones and serum and urinary calcium

Serum and urinary calcium levels increased after starting treatment with eldecalcitol and alfacalcidol, and returned to baseline levels within 1 month after the study period. Eldecalcitol treatment suppressed serum $1,25(OH)_2D_3$ by about 50%, while alfacalcidol did not suppress serum $1,25(OH)_2D_3$. Serum intact PTH was suppressed by alfacalcidol, but the suppression by eldecalcitol was less than that by alfacalcidol as reported previously [31] (Fig. 4).

Fractures

New vertebral fractures occurred in 2 patients (2/128, 1.6%) in the eldecalcitol group and in 3 patients (3/121, 2.5%) in the alfacalcidol group during the 12-month study period. Non-vertebral fractures occurred at the forearm, patella, ankle bone, and instep bone in 4 patients (4/121, 3.3%) in the alfacalcidol group, whereas none occurred in the eldecalcitol group. We did not conduct statistical test for this end point, because of the small subject number and short study period for evaluating the effect on fracture prevention.

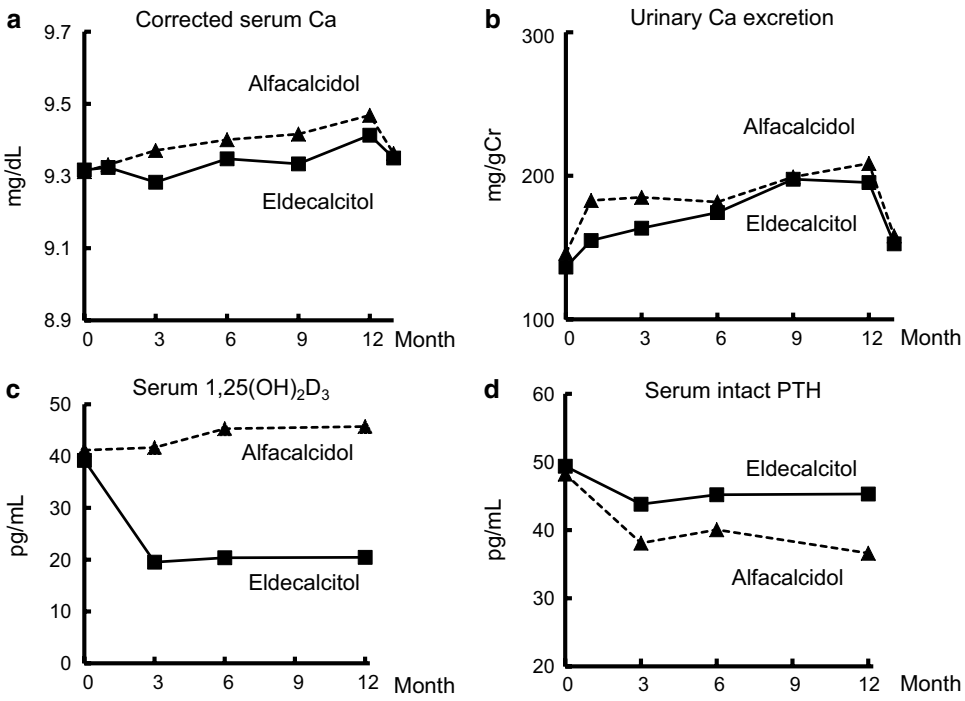

Fig. 4 Changes in **a** serum and **b** urinary calcium levels in patients given eldecalcitol and alfacalcidol for 12 months and 1 month after the study. Change in **c** serum $1,25(OH)_2D_3$ and **d** serum intact PTH levels in patients given eldecalcitol and alfacalcidol for 12 months. Data are mean values

Adverse events

Adverse events with more than 5% incidence in either of the two groups are listed in Table 2. There was no difference in the incidence of any adverse events between the two groups. Patients with transient hypercalcemia over 10.4 mg/dL at least once during the study numbered 8 in the eldecalcitol group and 11 in the alfacalcidol group. Patients in the eldecalcitol group were further divided by tertiles of baseline serum 25(OH)D and dietary calcium intake (Table 2). In this ad hoc analyses, the cutoff value for serum calcium was 10.4 mg/dL and that for urinary calcium was 300 mg/gCr. There was no significant difference in the incidence of hypercalcemia and hypercalciuria among the tertiles of 25(OH)D level. Number of patients with corrected serum calcium over 10.4 mg/dL at least once during the study period was lowest in the lower tertile and highest in the upper tertile of calcium intake. The incidence of increase in corrected serum calcium over 0.5 mg/dL was higher in the lower tertile than the upper tertile of calcium intake. The incidence of increase in urinary calcium excretion over 300 mg/gCr at least once or on two consecutive time points was again higher in the lower tertile than the upper tertile of calcium intake. In addition, more patients in the lower tertile of calcium intake showed increase in serum creatinine over 0.3 mg/dL.

Discussion

Calcium intake and serum 25(OH)D are the important factors for prevention of osteoporosis. The baseline serum 25(OH)D and daily calcium intake in Chinese osteoporotic patients in the present study were far less than the international recommendation level, as in the previous reports in China [9, 38]. It is interesting to note that the subgroup analysis of BMD by tertiles of baseline serum 25(OH)D (upper tertile ≥ 45.0 nmol/L, lower tertile < 30.0 nmol/L) and dietary calcium intake (upper tertile ≥ 595 mg/day, lower tertile < 371 mg/day) showed a tendency that the less the serum 25(OH)D level and dietary calcium intake, the lower was the BMD at all the measured sites in this study population.

In the present study, baseline urinary calcium excretion tended to be lower in the lower tertile of calcium intake, and baseline serum calcium tended to be lower in the lower tertiles of serum 25(OH)D and calcium intake. In contrast, baseline intact PTH tended to be higher in the lower tertile of calcium intake. Thus, it is plausible to speculate that, with very low calcium intake (less than 371 mg/day in the lower tertile), parathyroid hormone secretion was stimulated with a marginal reduction in serum calcium level. All these changes aggravate bone loss and enhance the development

Table 2 Safety analysis

Incidence of adverse events	Eldecalcitol ($n=136$)		Alfacalcidol ($n=127$)
General			
Any adverse events	114 (83.8%)		107 (84.3%)
Any serious adverse events	19 (14.0%)		14 (11.0%)
Death	0 (0.0%)		0 (0.0%)
Discontinued due to adverse events	3 (2.2%)		8 (6.3%)[a]
Adverse events with incidence rate > 5%			
Upper respiratory tract infection	26 (19.1%)		30 (23.6%)
Urinary tract infection	11 (8.1%)		13 (10.2%)
Nasopharyngitis	9 (6.6%)		10 (7.9%)
Chronic gastritis	10 (7.4%)		3 (2.4%)
Abdominal distension	8 (5.9%)		5 (3.9%)
Nausea	7 (5.1%)		4 (3.1%)
Toothache	7 (5.1%)		2 (1.6%)
Diarrhea	5 (3.7%)		9 (7.1%)
Back pain	13 (9.6%)		11 (8.7%)
Arthralgia	12 (8.8%)		9 (7.1%)
Pain in extremity	10 (7.4%)		4 (3.1%)
Musculoskeletal discomfort	7 (5.1%)		2 (1.6%)
Dizziness	7 (5.1%)		10 (7.9%)
Renal cyst	6 (4.4%)		7 (5.5%)
Cough	9 (6.6%)		10 (7.9%)
Serum and urinary calcium increase			
Serum calcium > 11.0 mg/dL	0 (0.0%)		1(0.8%)
Serum calcium > 10.4 mg/dL	8 (5.9%)		11 (8.7%)
Urinary calcium > 400 mg/gCr on two consecutive time points	5 (3.7%)		3 (2.4%)
Serum creatinine change from baseline > 0.3 mg/dL	4 (2.9%)		0 (0.0%)
Subgroup analysis by baseline serum 25(OH)D in the eldecalcitol group	Lo ($n=36$)	Mid ($n=57$)	Hi ($n=42$)
Serum calcium > 10.4 mg/dL	2 (5.6%)	4 (7.0%)	2 (4.8%)
Corrected serum Ca change from baseline > 0.5 mg/dL	15 (41.7%)	20 (35.1%)	14 (33.3%)
Urinary calcium > 300 mg/gCr	11 (30.6%)	18 (31.6%)	12 (28.6%)
Urinary calcium > 300 mg/gCr on two consecutive time points	4 (11.1%)	6 (10.5%)	7 (16.7%)
Serum creatinine change from baseline > 0.3 mg/dL	2 (5.6%)	1 (1.8%)	1 (2.4%)
Subgroup analysis by baseline calcium intake in the eldecalcitol group	Lo ($n=52$)	Mid ($n=40$)	Hi ($n=44$)
Serum calcium > 10.4 mg/dL	1 (1.9%)	3 (7.5%)	4 (9.1%)
Corrected serum Ca change from baseline > 0.5 mg/dL	23 (44.2%)	19 (47.5%)	8 (18.2%)
Urinary calcium > 300 mg/gCr	18 (34.6%)	13 (32.5%)	10 (22.7%)
Urinary calcium > 300 mg/gCr on two consecutive time points	7 (13.5%)	7 (17.5%)	3 (6.8%)
Serum creatinine change from baseline > 0.3 mg/dL	2 (3.8%)	2 (5.0%)	0 (0.0%)

Data are compiled using ICH Medical Terminology MedDRA Ver 18.1. All data are reported as number (percentage). The cutoff values for each subgroup are defined as the tertile of the whole study population

[a]The reason for an additional subject who discontinued due to adverse events was that the investigator reported an adverse event of this subject in this category, though the main reason for discontinuation was violation of exclusion criteria

of osteoporosis. These results give us an important message that vitamin D supply and calcium intake influence bone mass accrual, and that the importance of their sufficiency should be emphasized to prevent osteoporosis as mentioned in the guideline in China [39].

The present study demonstrated that eldecalcitol increased lumbar and hip BMD almost similarly across a wide range of serum 25(OH)D and daily calcium intake. Although the possibility cannot be ruled out that a part of the effect of eldecalcitol on BMD may be due to supplementary

effect on vitamin D insufficiency/deficiency, the effect of eldecalcitol was superior to alfacalcidol at any site of BMD measurement. BMD increase at the lumbar spine and femoral neck tended to be even higher among subjects with low calcium intake. In a previous study in Japan in which the effect of eldecalcitol was compared with that of alfacalcidol on BMD and fractures, the mean daily calcium intake of the subjects was over 700 mg, and serum 25(OH)D was maintained above 50 nmol/L in 92% of the participants [31], which were much higher than those among subjects in the present study. In that previous study, eldecalcitol increased BMD in the lumbar spine by 2.9% and in the total hip by 1.3% in 12 months [31]. Thus, although daily calcium intake and serum 25(OH)D were much lower among subjects in the present study, the increase in BMD at both the lumbar spine and total hip was surprisingly similar. These results are consistent with the notion that eldecalcitol can increase BMD across wide range of vitamin D status or nutritional calcium intake, and that eldecalcitol can be a good treatment of choice in osteoporotic patients with low vitamin D or calcium supply. Because the incidence of vertebral fracture was reduced in eldecalcitol-treated group compared to that in alfacalcidol-treated group in a previous study in Japan, it is plausible to speculate that eldecalcitol may be able to reduce fracture incidence as well in Chinese osteoporotic patients regardless of calcium intake or serum 25(OH)D level.

With regard to safety, in eldecalcitol-treated patients with low calcium intake, the incidence of hypercalciuria and the increase in serum calcium were higher, whereas the incidence of hypercalcemia was less than those in the eldecalcitol-treated group with higher calcium intake. Because serum PTH was higher at the baseline among subjects with low calcium intake, the responsiveness to eldecalcitol in increasing intestinal calcium absorption may be enhanced. As a result, their response to eldecalcitol in increasing urinary calcium excretion and serum calcium may be exaggerated. However, because baseline serum calcium was lower in patients with low calcium intake, less number of patients developed hypercalcemia after eldecalcitol treatment.

The present study has limitations. First, the study was not large enough to see statistical difference of fracture incidence or other end points between subgroups. Second, the study period was short, and the effect of longer treatment with eldecalcitol in a larger number of subjects is necessary to examine the effect of eldecalcitol on fractures. Third, the present study does not have enough number of subjects with sufficient vitamin D status. As a result, the present study could not directly compare the effect of eldecalcitol between subjects with vitamin D sufficiency and insufficiency.

In conclusion, the present study demonstrates that baseline BMD is lower in patients with low calcium intake and low serum 25(OH)D level. Eldecalcitol can effectively increase BMD at the lumbar spine, total hip, and femoral neck regardless of calcium intake or serum 25(OH)D level in Chinese osteoporotic patients without vitamin D or calcium supplementation. From these results, it is suggested that eldecalcitol is effective in increasing BMD of osteoporotic patients with vitamin D deficiency and low calcium intake without vitamin D or calcium supplementation.

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Compliance with ethical standards

Conflict of interest Weibo Xia serves as a consultant for Chugai Pharmaceutical Co., Ltd. Toshio Matsumoto serves as a consultant for Chugai Pharmaceutical Co., Ltd. and Amgen Inc. Tsuyoshi Kobayashi and Satomi Uehara are employees of Chugai Pharmaceutical Co., Ltd. Yan Jiang, Hai Tang, Xinlong Ma, Qun Cheng, Hua Lin, Xiaolan Jin, Zhenlin Zhang, Wei Yu, and Shuli He declare that they have no conflict of interest. This study was funded by Chugai Pharmaceutical Co., Ltd.

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