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ORIGINAL ARTICLE

Factors associated with inadequate responses to risedronate in Japanese patients with osteoporosis

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Abstract

Factors associated with an inadequate response (IR) to bisphosphonates have been reported in many countries, but not in Japan, where the approved dose is half the global dose. We analyzed factors associated with IR to risedronate in Japanese patients with osteoporosis. This was a post hoc analysis of 1261 Japanese osteoporosis patients who received risedronate for 1 year in phase III trials. IR was defined as more than one new vertebral fracture (VF) and/or negative change in lumbar spine bone mineral density (BMD) at 1 year. Various baseline and follow-up variables were examined for potential contribution to IR. Of the 1261 subjects, 118 exhibited an IR. At baseline, IR was associated with a higher BMD, lower levels of bone turnover markers (BTM) (serum bone-specific alkaline phosphatase, urinary N-terminal telopeptide of type 1 collagen and C-terminal telopeptide of type 1 collagen), and serum 25-hydroxyvitamin D [25(OH)D] below 16 ng/mL. BTM changes were blunted at 6 months in subjects with IR. On simple regression analysis, all the above variables and poor drug adherence were associated with an IR. On multivariate regression analysis, factors associated with IR were high BMD, vitamin D deficiency at baseline and low BTM at baseline, or a decreased BTM response at 6 months. Low serum 25(OH)D and BTM as well as high BMD at baseline were independent predictors of an IR to risedronate in Japan. These results emphasize the importance of the assessment of serum 25(OH)D and BTM in the management of osteoporosis with bisphosphonates.

Keywords Risedronate · Bone mineral density · Fracture · Bone turnover markers · 25(OH)D

Introduction

The oral bisphosphonate, risedronate, is widely used for the treatment of osteoporosis. Its anti-fracture efficacy and positive effects on bone mineral density (BMD) are well established [1]. However, it has been recognized that some subjects do not adequately respond to bisphosphonates, including risedronate, as well as to other anti-osteoporotic medications. The reported rates of inadequate response (IR) to bisphosphonates vary greatly, depending on the bisphosphonate and the definition of IR used, and range from less than 10% to above 50% [2–10]. Most studies have defined IR according to the occurrence of new fractures [3, 4, 6, 8, 9], or BMD loss above a certain threshold [10], or a combination of the two [2, 5, 7]. Although the primary aim of anti-osteoporosis treatment is to prevent fractures, fracture prevention is difficult to assess in the clinical setting. Therefore, BMD and bone turnover markers (BTM) have been used as surrogate endpoints to monitor the pharmaceutical treatment of osteoporosis in both clinical settings and trials. Virtually all the anti-osteoporotic agents with proven anti-fracture efficacy have been shown to significantly increase BMD in clinical trials. The reported mean increase in lumbar spine BMD (LsBMD) by risedronate after 1 year is 2.6–3.5% at a dose of 5 mg/day or equivalent [11–13] and 2.2% at a dose of 2.5 mg/day [11]. However, in one study, 24.4% of the subjects lost LsBMD after 1 year of treatment with risedronate, despite a mean LsBMD increase of 2.6% [13]. In studies of other bisphosphonates, 9–13% of the subjects lost LsBMD after 1 year [13, 14]. Although the precise significance of BMD loss has been debated [15–17], it is generally thought that the patients receiving bisphosphonate treatment who gain BMD have a reduced fracture risk compared to those with BMD loss during the treatment [18–21]. In a study using risedronate, Watts et al. [18] reported that patients who

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lost BMD were at a greater risk of vertebral fracture (VF) than those who gained BMD, although greater increases in BMD were not associated with a further decrease in VF risk. Several factors have been reported to be associated with an IR to bisphosphonates, including poor adherence [3, 4], vitamin D inadequacy [2, 3, 5, 6] and comorbidities [9].

In Japan, the approved doses of risedronate and alendronate for the treatment of osteoporosis are half of the generally used global dose. The IR for bisphosphonates has not been systematically analyzed in Japan. Using data from phase III risedronate clinical trials conducted in Japan, we have previously reported that the comorbidities of diabetes mellitus, hypertension and dyslipidemia did not significantly affect BMD or the BTM response [22]. Using overlapping data obtained from phase III risedronate clinical trials, Mawatari et al. recently reported that a low baseline serum 25-hydroxyvitamin D [25(OH)D] level and high BMD are associated with a reduced BMD response [23]. However, they did not study BTM at baseline or at follow-up. In the present study, we analyzed factors associated with an IR to risedronate in Japanese patients with osteoporosis, including BTM and drug adherence.

Materials and Methods

Data included in the analysis

The present analysis was conducted using the combined data from two randomized, double-blind phase III trials of risedronate (CCT-101 study and CCT-301 study) [24, 25] that were conducted at multiple medical institutions in Japan between November 2002 and August 2011. In the CCT-101 study (48 weeks of treatment), eligible patients were randomly assigned to receive either a once-weekly 17.5 mg dose or a once-daily 2.5 mg dose of risedronate. In the CCT-301 study (12 months of treatment), the eligible patients were randomly assigned to receive either a once-monthly 75 mg dose or a once-daily 2.5 mg dose of risedronate. In both studies, study drug blinding was achieved using a double-dummy technique with active drugs and corresponding placebo tablets.

All patients were administered a supplement of 1.54 g of calcium lactate (equivalent to 200 mg elemental calcium) throughout the study period. The daily dose of calcium was based on the results of the National Nutrition Survey conducted by the Ministry of Health, Labour and Welfare (recommended daily allowance of calcium for Japanese persons, 600 mg; actual intake, 585 mg; average values from 1995) and the necessary amount in the elderly estimated in a calcium balance study (700–800 mg) [26]. Vitamin D was not given as a supplement in the two studies. Throughout the study period, the concomitant use of any drugs known to affect bone metabolism was prohibited. Informed consent was obtained from all individual participants included in the study.

Subjects

A previous post hoc analysis [23] of three phase III trials (CCT-003, CCT-101 and CCT-301 studies) included data from 1447 osteoporosis patients who had received risedronate within one of the risedronate trials and had their baseline LS-BMD determined.

In the present study, all patients in the CCT-003 study were excluded as their 25(OH)D level was not determined. Hence, this post hoc analysis included combined data from 1261 patients with osteoporosis who received risedronate treatment for 48 weeks (CCT-101 study) or 12 months (CCT-301 study). Ambulatory patients of either sex, older than 50 years of age and with involutional osteoporosis were eligible if they met the diagnostic criteria for primary osteoporosis by the Committee of the Japanese Society for Bone and Mineral Research (JSBMR) [27]. Eligible women were postmenopausal and at least 2 years after the last menstrual period. The exclusion criteria were as follows: any secondary osteoporosis or other disease known to cause reduced bone mass, any radiographic findings that might affect vertebral integrity, recent use of drugs known to affect bone metabolism, serious renal, hepatic, cardiac or gastrointestinal disease, drug hypersensitivity, malignant tumor under treatment with antitumor agents, history of radiotherapy to the lumbar spine or pelvis, or history of treatment with risedronate.

Study design

In the CCT-101 and CCT-301 studies, the primary efficacy endpoint was the percentage change in the mean L_2–L_4 BMD from baseline to the time of final evaluation. In the present study, the following were used as potential prognostic factors for logistic regression model analyses: age, height, body mass index (BMI), sex, comorbid disease [diabetes mellitus (DM), hypertension (HT) or dyslipidemia (DL)], prevalent VF, bone resorption markers [urinary N-terminal telopeptide of type 1 collagen (NTX) and the C-terminal telopeptide of type 1 collagen (CTX)] at baseline, as well as the percentage change from baseline to 6 months, bone formation markers [serum bone-specific alkaline phosphatase (BAP)] at baseline and percentage change from baseline to 6 months, serum levels of 25-hydroxyvitamin D [25(OH)D], L_2–L_4 BMD at baseline, and adherence.

In CCT-101, the L_2–L_4 BMD was determined at baseline and after 12, 24, 36 and 48 weeks of treatment, or at the time of withdrawal from the study, by dual-energy X-ray absorptiometry (DXA) using QDR, XR or DPX type instruments. In

CCT-301, it was also determined at baseline, after 6 and after 12 months of treatment, or at the time of withdrawal from the study, by DXA using QDR type instruments. These L_2–L_4 BMD results were assessed by a specialized central review committee that was blinded to the patient information. The presence or absence of comorbid DM, HT or DL was recorded based on the diagnosis of the attending physician at the initiation of each study.

Chest and lumbar spine X-rays were taken at baseline and at the end of the trial. A specialized central review committee determined whether there were pre-existing or new fractures and also whether a worsening of pre-existing fractures had occurred. Vertebral fractures were judged based on the JSBMR diagnostic criteria for primary osteoporosis [27]. An incident of vertebral fracture was considered to have occurred when the ratio of the central to anterior vertebral height (*C*/*A*) was < 0.8; the ratio of the central to posterior vertebral body height (*C*/*P*) was < 0.8; the ratio of the anterior to posterior vertebral height (*A*/*P*) was < 0.75; or the *A*, *C* and *P* heights were decreased by at least 20% from their baseline values. In trial CCT-101, a pre-existing vertebral fracture was considered to have worsened if the *C*/*A*, *C*/*P* or *A*/*P* had decreased by 20% or more from the baseline values [28]. In trial CCT-301, a semi-quantitative assessment method was used to detect the worsening of an existing fracture, which was based on whether *A*, *C* or *P* was decreased by at least 20% (or 4 mm) from their baseline values. In such a case, the condition was considered to have progressed by one grade or more [29].

Biochemical markers of bone turnover (NTX, CTX and BAP) were assessed at baseline and after 4, 12, 24, 36 and 48 weeks of treatment in CCT-101, and at baseline and after 1, 3, 6, 9 and 12 months, or upon study discontinuation, in CCT-301. Urinary NTX and CTX were measured by enzyme-linked immunosorbent assay (ELISA). All urinary parameters were corrected for creatinine excretion. Serum BAP was determined by enzyme immunoassay. The serum levels of 25(OH)D were determined using a radioimmunoassay method.

Adherence was calculated by the actual number of tablets taken divided by the scheduled number of tablets. In the CCT-101 study, compliance was collected categorically on every visit. The compliance categories were more than or equal to 90%, more than or equal to 67% and less than 90%, more than or equal to 50% and less than 67%, more than or equal to 25% and less than 50%, and less than 25%. The average of every range was regarded as the nominal compliance rate for each category. Adherence was calculated by the formula shown below.

$$\begin{aligned}\text{Adherence} = {} & \Sigma\,[\text{nominal compliance}] \\ & \times\,[\text{days between the sequential visits}]\,/ \\ & ([\text{the last observation date}] \\ & -\,[\text{the start date of treatment}]).\end{aligned}$$

In the CCT-301 study, the number of tablets taken was recorded. Therefore, the adherence was calculated by the following formula:

$$\begin{aligned}\text{Adherence (daily)} = {} & [\text{the number of tablets taken}]/ \\ & ([\text{the last observation date}] \\ & -\,[\text{the start date of treatment}]) \\ & \times 100\,(\%).\end{aligned}$$

$$\begin{aligned}&\text{Adherence (monthly)} \\ &= [\text{the number of tablets taken}] \\ &\quad \times\,[30.4375 :\ \text{average of the number of months}]/ \\ &\quad ([\text{the last observation date}] - [\text{the start date of treatment}]) \\ &\quad \times 100\%).\end{aligned}$$

In the monthly arm, when the observation was discontinued before the next scheduled visit, the adherence was greater than 100%, because the first dosing date was the treatment start date. In such a case, the adherence was considered to be 100%.

The patients were classified as inadequate responders to risedronate in the presence of at least one of the following criteria: (1) the BMD percentage change from baseline was below 0% (BMD loss); or (2) new vertebral fractures and worsening of existing fractures (fracture).

Statistical analyses

The basal urinary NTX, urinary CTX and serum BAP levels were transformed into dichotomous variables with cutoff values of the mean + 1.0 SD for Japanese premenopausal women: urinary NTX at 35.3 nmol BCE/mmol Cr, urinary CTX at 184.1 μg/mmol Cr and serum BAP at 21.1 U/L [30]. The subjects were categorized into three subgroups according to the two bone resorption markers (BRM); low BRM: both urinary NTX and urinary CTX less than mean + 1.0 SD, mid BRM: only one of urinary NTX or urinary CTX less than mean + 1.0 SD, high BRM; neither urinary NTX nor urinary CTX less than mean + 1.0 SD. Basal serum 25(OH)D levels were transformed into dichotomous variables with cutoff values of the first quartile of the study population set at serum 25(OH)D at 16 ng/mL.

Furthermore, the percentage changes from baseline of the biochemical markers of bone turnover at 6 months were transformed into dichotomous variables − 25% [30], with minimum significant change (MSC) values of − 23.1, − 27.3 and − 23.5% for serum BAP, urinary NTX and urinary CTX, respectively [30]. The subjects were categorized into three subgroups according to the percentage change from baseline of the two BRMs: (1) normal BRM response (BRMR): both the urinary NTX and urinary

CTX were decreased more than MSC, (2) mid-BRMR: only one of the two urinary factors NTX or urinary CTX was decreased more than MSC, and (3) low BRMR; neither urinary NTX nor urinary CTX was decreased more than MSC.

The responders (Rs) and inadequate responders (IRs) were further divided into subgroups of BMD loss and Fracture; the differences in the characteristics between these subgroups were examined. Multiple repeat pairwise comparisons were made among these three groups (responders, BMD loss and fracture). The significant level for the p values containing corrected p values by the Tukey–Kramer method was 0.05, while the significant level for the p values by the Bonferroni method was 0.05/3.

Logistic regression models were constructed, with response to risedronate (i.e., IR or R) as the binary response variable and prognostic factors as the regression variables. First, simple logistic regression models were constructed with each prognostic factor as an independent variable, then their regression coefficients and p values were calculated. For the independent variables that could be translated into a dichotomous variable with the cut-off values mentioned above, regression models were also constructed, with the dichotomous variables as the regressor. Where both the original variable and the translated variable were available, the variable with the smaller p value was selected as the candidate regressor in a multiple regression model. Then, the correlation coefficients between the prognostic factors were calculated. When the combination of prognostic factors was strongly correlated ($r > 0.8$), the combined variables of two prognostic factors were generated to avoid multicollinearity. Finally, multiple logistic regression models with the remaining factors as candidate regressors were constructed, and the odds ratios and p values of the regression coefficients were calculated. It was considered that the regressors with $p < 0.05$ were relevant. All the statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

Inadequate responders (IRs) versus responders (Rs)

Of the 1261 subjects, we identified 118 IRs (9.4%) based on the criteria of either a negative BMD response at 12 months or at least one new VF at 12 months. The baseline characteristics of IRs and Rs are listed in Table 1. Of the 118 IRs, 15 had one or more VFs: 12 subjects had one VF and three subjects had two VFs. One subject with one VF also lost BMD; the other 14 subjects with VFs gained BMD at 12 months. Of the 118 IRs, 103 subjects showed BMD loss at 12 months, but did not have VF. Of these 103 subjects, 60 also had negative BMD changes at 6 months. At 6 months, a total of 151 subjects had negative BMD change, among whom 91 had gained BMD at 12 months. The distribution of BMD change of the 1261 subjects at 12 months is shown in Fig. 1.

Within the IRs, compared with the BMD loss group, the VF group had a higher rate of prevalent VF at baseline and positive BMD responses at both 6 and 12 months (Table 1). Otherwise, the two groups were not significantly different. Thus, we compared the IRs as a whole with the Rs. The IRs had lower basal BAP, NTX and CTX, and more subjects had basal BTM of less than the mean of + 1.0 SD for Japanese premenopausal women. Changes in all BTM at 6 months and 12 months were all reduced in the IRs compared with the Rs. When using the cut-off of 25% or MSC, a greater proportion of subjects did not exhibit significant BTM changes at 6 months in the IR group. The serum 25(OH)D level was not different between the groups, but in the IR group there were more subjects with a serum 25(OH)D level below 16 ng/mL. Adherence was not different between the IRs and Rs, but the BMD loss group had a lower adherence than the Rs. As a whole, the IRs had a higher BMD at baseline and a lower increase in BMD at 6 months compared with the Rs.

Simple logistic regression analysis

As shown in Table 2, we identified five baseline factors that were associated with IR: low serum 25(OH)D level (< 16 ng/mL), low serum BAP level (< 1.0 SD), low urinary NTX level (< 1.0 SD), low urinary CTX level (< 1.0 SD) and high BMD. As follow-up factors, low adherence and a diminished BTM at 6 months were associated with IR.

The serum 25(OH)D level was below 16 ng/mL in 272 subjects, 38 of whom (14.0%) were IRs, whereas among 989 subjects with a basal serum 25(OH)D level of greater than 16 ng/mL, only 80 (8.1%) were IRs, which was significantly different ($p = 0.0032$). Likewise, among subjects with a lower BAP ($n = 290$), 43 (14.8%) were IRs, whereas in subjects with a higher BAP ($n = 971$), only 75 (7.7%) were IRs ($p = 0.0003$). In the low CTX group, 15.7% (41/261) were IRs, whereas in the higher CTX group, only 7.7% (77/1000) were IRs ($p < 0.0001$). In the low NTX group, 15.2% (33/217) were IRs, whereas in the higher NTX group, only 8.1% (85/1044) were IRs ($p < 0.0001$). As CTX and NTX are both bone resorption markers and highly correlated ($r = 0.806$, $p < 0.0001$) with each other, we also analyzed their combined influence. When the subjects were categorized into three subgroups according to the basal level of these two BRM, there were 143 subjects with both a low CTX and low NTX (Low BRM), 192 with only one low BRM (Mid BRM), and 926 subjects with both a higher CTX and NTX (high BRM) (Table 1). The IR rates of those three

Table 1 Characteristics of the study subjects

	Total	Responders	Inadequate responders			
			All	Fracture	BMD loss	
n	1261	1143	118	15	103	
Age (years)	67.7 ± 7.1	67.6 ± 7.0	68.8 ± 8.2	71.3 ± 9.6	68.5 ± 8.0	
		0.0826[*a]	*0.1310*[*c]	*0.1220*[*e]	*0.4938*[*g]	*0.3288*[*i]
Height (cm)	150.7 ± 6.0	150.6 ± 6.0	151.1 ± 5.9	148.0 ± 7.8	151.6 ± 5.4	
		0.0678[*a]	*0.3804*[*c]	*0.2177*[*e]	*0.2635*[*g]	*0.0804*[*i]
BMI (kg/m^2)	21.8 ± 2.9	21.7 ± 2.9	21.8 ± 3.0	20.5 ± 2.2	22.0 ± 3.0	
		0.1772[*a]	*0.8577*[*c]	*0.2239*[*e]	*0.7021*[*g]	*0.1530*[*i]
Female/male (%/%)	1234/27 (97.9/2.1)	1119/24 (97.9/2.1)	115/3 (97.5/2.5)	15/0 (100.0/0.0)	100/3 (97.1/2.9)	
		0.6275[*b]	*0.7344*[*d]	*1.0000*[*f]	*0.4837*[*h]	*1.0000*[*j]
DM (%)	57 (4.5)	48 (4.2)	9 (7.6)	0 (0.0)	9 (8.7)	
		0.1020[*b]	*0.1002*[*d]	*1.0000*[*f]	*0.0460*[*h]	*0.6011*[*j]
HT (%)	409 (32.4)	376 (32.9)	33 (28.0)	6 (40.0)	27 (26.2)	
		0.3084[*b]	*0.3026*[*d]	*0.5858*[*f]	*0.1872*[*h]	*0.3549*[*j]
DL (%)	432 (34.3)	387 (33.9)	45 (38.1)	3 (20.0)	42 (40.8)	
		0.1872[*b]	*0.3602*[*d]	*0.4096*[*f]	*0.1606*[*h]	*0.1593*[*j]
Prevalent VF	303 (24.1) [#]	274 (24.0) [¶]	29 (24.6)	10 (66.7)	19 (18.4)	
		0.0007[*b]	*0.9100*[*d]	*0.0006*[*f]	*0.2264*[*h]	*0.0003*[*j]
25(OH)D (ng/mL)	21.0 ± 6.6	21.1 ± 6.5	20.2 ± 7.3	21.7 ± 10.2	20.0 ± 6.8	
		0.2597[*a]	*0.1789*[*c]	*0.9252*[*e]	*0.2519*[*g]	*0.6127*[*i]
BAP (U/L)	27.9 ± 9.6	28.2 ± 9.5	25.4 ± 9.8	30.4 ± 14.6	24.6 ± 8.7	
		0.0008[*a]	*0.0023*[*c]	*0.6335*[*e]	*0.0008*[*g]	*0.0698*[*i]
NTX (nmol BCE/mmol CRN)	55.4 ± 23.0	55.9 ± 22.9	50.3 ± 23.5	54.2 ± 25.6	49.8 ± 23.3	
		0.0354[*a]	*0.0129*[*c]	*0.9601*[*e]	*0.0269*[*g]	*0.7604*[*i]
CTX (μg/mmol CRN)	296.2 ± 143.2	299.3 ± 142.6	266.1 ± 146.4	306.5 ± 187.8	260.2 ± 139.5	
		0.0283[*a]	*0.0164*[*c]	*0.9794*[*e]	*0.0216*[*g]	*0.4698*[*i]
L_2–L_4 BMD (g/cm^2)	0.650 ± 0.073	0.648 ± 0.073	0.668 ± 0.067	0.636 ± 0.056	0.673 ± 0.068	
		0.0041[*a]	*0.0057*[*c]	*0.7789*[*e]	*0.0036*[*g]	*0.1580*[*i]
% BMD change at 6 months	4.69 ± 4.02	5.14 ± 3.77	0.27 ± 3.71	4.70 ± 4.16	− 0.37 ± 3.18	
		< 0.0001[*a]	*< 0.0001*[*c]	*0.8923*[*e]	*< 0.0001*[*g]	*< 0.0001*[*i]
% BMD change at 12 months	5.69 ± 4.31	6.40 ± 3.72	− 1.23 ± 3.37	5.19 ± 4.51	− 2.17 ± 1.80	
		< 0.0001[*a]	*< 0.0001*[*c]	*0.4025*[*e]	*< 0.0001*[*g]	*< 0.0001*[*i]
25(OH)D < 16 ng/mL (%)	272 (21.6)	234 (20.5)	38 (32.2)	6 (40.0)	32 (31.1)	
		0.0088[*b]	*0.0046*[*d]	*0.0995*[*f]	*0.0165*[*h]	*0.5577*[*j]
BAP < 1.0 SD (%)	290 (23.0)	247 (21.6)	43 (36.4)	3 (20.0)	40 (38.8)	
		0.0006[*b]	*0.0005*[*d]	*1.0000*[*f]	*0.0002*[*h]	*0.2504*[*j]
NTX < 1.0 SD (%)	217 (17.2)	184 (16.1)	33 (28.0)	3 (20.0)	30 (29.1)	
		0.0045[*b]	*0.0020*[*d]	*0.7212*[*f]	*0.0016*[*h]	*0.5534*[*j]
CTX < 1.0 SD (%)	261 (20.7)	220 (19.2)	41 (34.7)	4 (26.7)	37 (35.9)	
		0.0005[*b]	*0.0002*[*d]	*0.5079*[*f]	*0.0002*[*h]	*0.5722*[*j]
BRM						
High BRM (%)	926 (73.4)	855 (74.8)	71 (60.2)	10 (66.7)	61 (59.2)	
Mid BRM (%)	192 (15.2)	172 (15.0)	20 (16.9)	3 (20.0)	17 (16.5)	
Low BRM (%)	143 (11.3)	116 (10.1)	27 (22.9)	2 (13.3)	25 (24.3)	
		0.0009[*b]	*0.0003*[*d]	*0.0590*[*f]	*0.0002*[*h]	*0.7329*[*j]
Adherence (%)	96.7 ± 5.6	97.0 ± 5.0	95.6 ± 9.1	96.7 ± 2.8	95.5 ± 9.6	
		0.0245[*a]	*0.1020*[*c]	*0.9600*[*f]	*0.0181*[*g]	*0.7293*[*i]
% BAP change at 6 months	− 28.4 ± 20.0	− 29.7 ± 18.8	− 15.8 ± 25.6	− 21.4 ± 35.8	− 15.0 ± 23.8	
		< 0.0001[*a]	*< 0.0001*[*c]	*0.2351*[*e]	*< 0.0001*[*g]	*0.4536*[*i]

Table 1 (continued)

	Total	Responders	Inadequate responders			
			All	Fracture	BMD loss	
% BAP change at 12 months	− 27.4 ± 21.3	− 29.0 ± 20.0	− 12.4 ± 27.4	− 21.9 ± 28.5	− 11.1 ± 27.1	
		< 0.0001[*a]	*< 0.0001*[*c]	*0.3939*[*e]	*< 0.0001*[*g]	*0.1413*[*i]
% CTX change at 6 months	− 52.1 ± 33.8	− 54.2 ± 31.0	− 31.5 ± 49.8	− 21.3 ± 76.6	− 33.0 ± 44.9	
		< 0.0001[*a]	*< 0.0001*[*c]	*0.0004*[*e]	*< 0.0001*[*g]	*0.4068*[*i]
% CTX change at 12 months	− 52.4 ± 36.1	− 54.6 ± 32.9	− 31.0 ± 54.2	− 29.0 ± 65.6	− 31.3 ± 52.7	
		< 0.0001[*a]	*< 0.0001*[*c]	*0.0153*[*e]	*< 0.0001*[*g]	*0.9696*[*i]
% NTX change at 6 months	− 41.5 ± 26.8	− 42.9 ± 25.6	− 28.3 ± 33.9	− 25.5 ± 37.7	− 28.7 ± 33.5	
		< 0.0001[*a]	*< 0.0001*[*c]	*0.0310*[*e]	*< 0.0001*[*g]	*0.8990*[*i]
% NTX change at 12 months	− 40.4 ± 27.9	− 42.2 ± 26.1	− 22.6 ± 37.5	− 22.1 ± 36.4	− 22.7 ± 37.8	
		< 0.0001[*a]	*< 0.0001*[*c]	*0.0127*[*e]	*< 0.0001*[*g]	*0.9957*[*i]
6-month BAP < − 25% (%)	477 (37.8)	404 (35.3)	73 (61.9)	7 (46.7)	66 (64.1)	
		< 0.0001[*b]	*< 0.0001*[*d]	*0.4182*[*f]	*< 0.0001*[*h]	*0.2564*[*j]
6-month BAP < MSC (%)	430 (34.1)	362 (31.7)	68 (57.6)	7 (46.7)	61 (59.2)	
		< 0.0001[*b]	*< 0.0001*[*d]	*0.2644*[*f]	*< 0.0001*[*h]	*0.4091*[*j]
6-month NTX < − 25% (%)	285 (22.6)	236 (20.7)	49 (41.5)	6 (40.0)	43 (41.7)	
		< 0.0001[*b]	*< 0.0001*[*d]	*0.1010*[*f]	*< 0.0001*[*h]	*1.0000*[*j]
6-month NTX < MSC (%)	318 (25.2)	265 (23.2)	53 (44.9)	6 (40.0)	47 (45.6)	
		< 0.0001[*b]	*< 0.0001*[*d]	*0.1319*[*f]	*< 0.0001*[*h]	*0.7849*[*j]
6-month CTX < − 25% (%)	201 (15.9)	153 (13.4)	48 (40.7)	5 (33.3)	43 (41.7)	
		< 0.0001[*b]	*< 0.0001*[*d]	*0.0424*[*f]	*< 0.0001*[*h]	*0.5872*[*j]
6-month CTX < MSC (%)	187 (14.8)	142 (12.4)	45 (38.1)	5 (33.3)	40 (38.8)	
		< 0.0001[*b]	*< 0.0001*[*d]	*0.0320*[*f]	*< 0.0001*[*h]	*0.7814*[*j]
6-month BRMR						
Normal BRMR (%)	885 (70.2)	828 (72.4)	57 (48.3)	8 (53.3)	49 (47.6)	
Mid BRMR (%)	247 (19.6)	223 (19.5)	24 (20.3)	3 (20.0)	21 (20.4)	
Low BRMR (%)	129 (10.2)	92 (8.0)	37 (31.4)	4 (26.7)	33 (32.0)	
		< 0.0001[*b]	*< 0.0001*[*d]	*0.0447*[*f]	*< 0.0001*[*h]	*0.9355*[*j]

BMI Body mass index, *DM* diabetes, *HT* hypertension, *DL* dyslipidemia, *VF* vertebral fracture, *BAP* bone-specific alkaline phosphatase, *NTX* N-terminal telopeptide of type 1 collagen, *CTX* C-terminal telopeptide of type 1 collagen, *BMD* bone mineral density, *BRM* Bone resorption markers, high BRM neither urinary NTX nor urinary CTX less than mean + 1.0 SD, *Mid BRM* only one of urinary NTX or urinary CTX less than mean + 1.0 SD, *Low BRM* both urinary NTX and urinary CTX less than mean + 1.0 SD, *MSC* minimum significant change, *BRMR* bone resorption markers response, *Normal BRMR* both urinary NTX and urinary CTX were decreased more than MSC, *Mid BRMR* only one of urinary NTX or urinary CTX was decreased more than MSC, *Low BRMR*; neither urinary NTX nor urinary CTX was decreased more than MSC

*p values are given in italics for all variables with the statistical analyses employed described below

[a]ANOVA: responders vs fracture vs BMD loss

[b]Fisher's exact test: responders vs fracture vs BMD loss

[c]t test: responders vs inadequate responders

[d]Fisher's exact test: responders vs inadequate responders

[e]Tukey–Kramer: responders vs fracture

[f]Bonferroni correction of Fisher's exact test: responders vs fracture

[g]Tukey–Kramer: responders vs BMD loss

[h]Bonferroni correction of Fisher's exact test: responders vs BMD loss

[i]Tukey–Kramer: fracture vs BMD loss

[j]Bonferroni correction of Fisher's exact test: fracture vs BMD loss

[#]The data were based on 1259 subjects

[†]The data were based on 1141 subjects

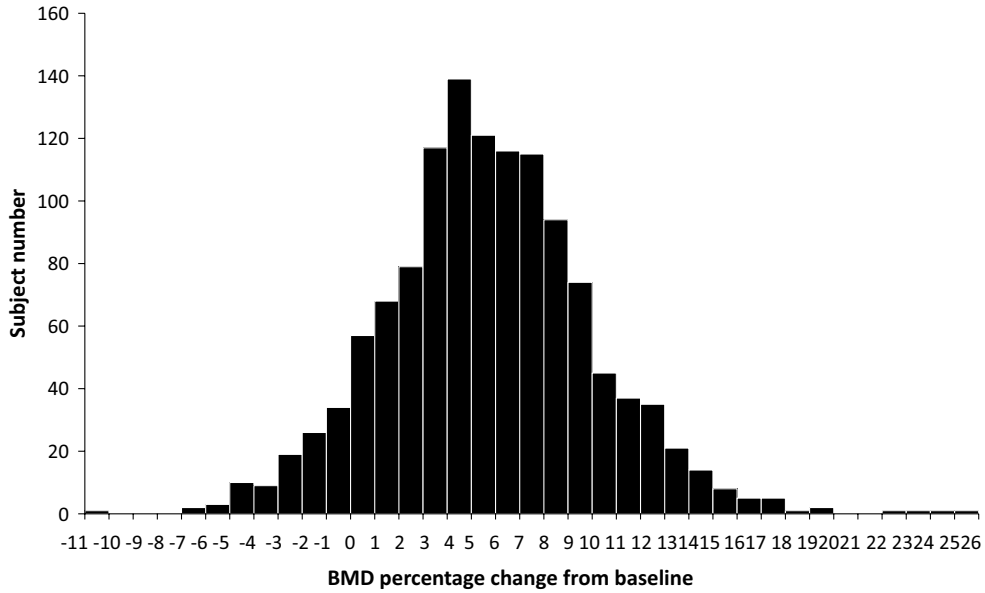

Fig. 1 Distribution of the L_2–L_4 BMD percentage change after 1 year of treatment with risedronate. *BMD* bone mineral density

subgroups were 18.9% (27/143), 10.4% (20/192) and 7.7% (71/926), respectively (p [trend] < 0.0001). The OR of the IRs for the Low BR vs Mid BR vs High BR was 1.640 (95% CI 1.293–2.082, $p < 0.0001$).

Reduced BTM responses at 6 months were associated with a higher rate of IR; whether using the cutoff of 25% or MSC, a reduced response was significantly associated with IR (Table 2). Two BRMs, urinary CTX and NTX, were categorized into three subgroups using the MSC cut-off: (1) a normal BRM response (normal BRMR), in which both the CTX and NTX were decreased more than MSC; (2) mid-BRMR, in which only one of the BRMs was decreased more than MSC; and (3) low BRMR, in which neither the CTX nor NTX was decreased more than MSC. As shown in Table 1, there were more subjects with a low BRMR among the IRs compared to Rs.

Multivariate logistic regression analysis

As shown in Table 3, all the baseline factors identified in the monovariate regression analysis were also associated with the IR obtained in the multivariate analysis using only baseline factors. When both NTX and CTX were used, only CTX was significantly associated with the IR in the multivariate analysis (Model A). Similar to the simple logistic analysis, when the levels of the two BRMs at baseline were categorized into three groups, mid and low BRMs were significantly associated with IR. Higher BMD at baseline was also associated with IR in our analysis. Low 25(OH)D, low BAP, low BRM and high BMD were all independently associated with IR, regardless of age and existing VF (Model B). Adherence was associated with IR, independent of all the baseline factors (Model C). However, when BTM changes were added to the models, as in Model D, the significant association with low basal BTM as well as adherence disappeared. Factors associated with IR were low serum 25(OH)D and high BMD at baseline, and a blunted BTM response at 6 months.

Discussion

In this study, low BTM was identified as a baseline predictor of IR to risedronate in Japanese subjects with osteoporosis, along with a low serum 25(OH)D level and high BMD. As follow-up factors, low adherence and decreased BTM responses were associated with IR. Similar to many previous reports, we defined IR by combining fracture and BMD loss [2, 5, 7, 31, 32]. As the primary aim of osteoporosis treatment is fracture prevention, some recent reports have chosen fracture as the sole constituent of IR [8, 9]. We chose not to take this position for several reasons. First, this is the first systematic study to examine IR to risedronate or any of the bisphosphonates in Japan, where the dose of bisphosphonates is half of the globally approved dose; the approved daily dose of risedronate for osteoporosis is 2.5 mg in Japan, but 5.0 mg elsewhere. Second, in the present analysis, only 15 out of 1261 subjects had any new fractures. Of these 15, only three had more than one fracture. According to the International Osteoporosis Foundation (IOF) committee definition, one fracture is not indicative of treatment failure [31]. If the IOF definition of treatment failure is applied

Table 2 Odds ratio (OR) for predicting an inadequate response to risedronate for the potential risk factors using simple logistic analysis

Variables	OR	95% confidence interval			*p* value
Age (1 year increase)	1.024	0.997	–	1.051	0.0857
BMI (one unit increase)	1.006	0.943	–	1.073	0.8570
Sex (female)	0.822	0.244	–	2.772	0.7521
DM (yes)	1.884	0.900	–	3.943	0.0929
HT (yes)	0.792	0.520	–	1.206	0.2771
DL (yes)	1.204	0.814	–	1.781	0.3518
Prevalent VF (yes)	1.031	0.664	–	1.602	0.8911
L_2–L_4 BMD (zero point one unit increase)	1.442	1.112	–	1.871	0.0058
25(OH)D (one unit increase)	0.980	0.951	–	1.009	0.1791
25(OH)D < 16 ng/mL	1.845	1.222	–	2.786	0.0036
BAP (one unit increase)	0.964	0.942	–	0.987	0.0022
BAP < 1.0 SD	2.080	1.393	–	3.104	0.0003
NTX (one unit increase)	0.988	0.978	–	0.997	0.0130
NTX < 1.0 SD	2.023	1.314	–	3.116	0.0014
CTX (one unit increase)	0.998	0.997	–	1.000	0.0163
CTX < 1.0 SD	2.234	1.488	–	3.354	0.0001
BRM (high BRM/mid BRM/low BRM) (one category change)	1.640	1.293	–	2.082	< 0.0001
Adherence (0–100%) (1% increase)	0.971	0.948	–	0.995	0.0170
Adherence (80–100%)*[1] (1% increase)	0.945	0.896	–	0.997	0.0389
6-month BAP < –25%	2.967	2.008	–	4.386	< 0.0001
6-month BAP < MSC	2.934	1.995	–	4.316	< 0.0001
6-month NTX < –25%	2.729	1.842	–	4.044	< 0.0001
6-month NTX < MSC	2.702	1.833	–	3.982	< 0.0001
6-month CTX < –25%	4.437	2.960	–	6.651	< 0.0001
6-month CTX < MSC	4.345	2.881	–	6.554	< 0.0001
6-month BRMR (normal BRMR/mid BRMR/low BRMR) (one category change)	2.324	1.833	–	2.947	< 0.0001

BMI Body mass index, *DM* diabetes, *HT* hypertension, *DL* dyslipidemia, *VF* vertebral fracture, *BAP* bone-specific alkaline phosphatase, *NTX* N-terminal telopeptide of type 1 collagen, *CTX* C-terminal telopeptide of type 1 collagen, *BMD* bone mineral density, *BRM* bone resorption markers, *High BRM* neither urinary NTX nor urinary CTX less than mean + 1.0 SD, *Mid BRM* only one of urinary NTX or urinary CTX less than mean + 1.0 SD, *Low BRM* both urinary NTX and urinary CTX less than mean + 1.0 SD, *MSC* minimum significant change, *BRMR* bone resorption markers response, *Normal BRMR* both urinary NTX and urinary CTX more than MSC, *Mid BRMR* only one of urinary NTX or urinary CTX more than MSC, *Low BRMR* neither urinary NTX nor urinary CTX more than MSC

*1 excluding 13 subjects with less than 80% adherence, $n = 1246$

to the subjects in this study, only 15 would fall into that category (three subjects with two fractures, five subjects with one fracture and more than a 5% BMD loss and/or less than a 25% decrease in BTM, and seven with more than a 5% BMD loss and less than a 25% decrease in BTM). An analysis of such a small number of subjects would not be clinically useful. We demonstrated that the 15 subjects with fracture were not very different from the other subjects with BMD loss, except for a higher rate of prevalent fractures at baseline and the lack of overall BMD loss. Indeed, with the use of risedronate, LsBMD increase was reported to be associated with a decreased number of VFs [33]. We chose 0% for the BMD change cutoff because we believe it to be a clinically meaningful number based on previous reports on risedronate [18] and other anti-osteoporosis medications, including other bisphosphonates [10, 21]. Unlike other bisphosphonate studies or trials, only 8.2% of subjects lost LsBMD at 12 months in the present analysis, which was much lower than the 24% reported in the FACT study for risedronate, despite the reduced dosage administered to our study subjects [13]. For alendronate, 11–13% of subjects are reported to lose LsBMD after 1 year [13, 34].

Many studies have demonstrated that vitamin D deficiency/insufficiency is associated with an IR to bisphosphonates and other anti-osteoporosis medications [2, 3, 5, 6, 23, 35, 36]. Using data that overlap with ours, Mawatari and others [23] recently reported that a basal serum 25(OH)D level less than 21 ng/ml was associated with a

Table 3 Odds ratio (OR) for predicting inadequate responses to risedronate for the potential risk factors using multivariate logistic analysis

	OR	95% confidence interval			*p* value	χ^2
Model A (baseline factors)						
BMD	1.391	1.056	–	1.832	0.0190	5.506
25(OH)D < 16 ng/mL	1.969	1.293	–	2.999	0.0016	9.973
BAP < mean + 1.0 SD	1.767	1.156	–	2.700	0.0085	6.916
NTX < mean + 1.0 SD	1.226	0.720	–	2.086	0.4532	0.563
CTX < mean + 1.0 SD	1.674	1.025	–	2.735	0.0395	4.241
Model B (baseline factors)						
MD	1.415	1.073	–	1.865	0.0139	6.046
25(OH)D < 16 ng/mL	1.970	1.293	–	3.000	0.0016	9.959
BAP < mean + 1.0 SD	1.759	1.151	–	2.690	0.0091	6.799
BRM (high BRM/mid BRM/low BRM) (one category change)	1.411	1.091	–	1.825	0.0088	6.866
Age	1.021	0.993	–	1.049	0.1379	2.201
Prevalent VF	0.911	0.573	–	1.446	0.6916	0.157
Model C (baseline factors + adherence)						
BMD	1.394	1.058	–	1.836	0.0181	5.590
25(OH)D < 16 ng/mL	1.910	1.249	–	2.921	0.0028	8.919
BAP < mean + 1.0 SD	1.847	1.204	–	2.834	0.0050	7.898
BRM (high BRM/mid BRM/low BRM) (one category change)	1.396	1.078	–	1.808	0.0114	6.398
Age	1.020	0.992	–	1.048	0.1590	1.984
Prevalent VF	0.906	0.569	–	1.442	0.6761	0.175
Adherence	0.973	0.949	–	0.997	0.0296	4.730
Model D (all factors)						
BMD	1.400	1.050	–	1.867	0.0220	5.245
25(OH)D < 16 ng/mL	2.070	1.337	–	3.206	0.0011	10.625
BAP < mean + 1.0 SD	1.348	0.850	–	2.138	0.2048	1.608
6-month BAP < MSC	2.003	1.298	–	3.092	0.0017	9.838
BRM (high BRM/mid BRM/low BRM) (one category change)	1.215	0.927	–	1.591	0.1577	1.996
6-month BRMR (normal BRMR/mid BRMR/low BRMR) (one category change)	1.920	1.471	–	2.506	< 0.0001	23.086
Adherence	0.984	0.960	–	1.010	0.2235	1.482
Age	1.028	1.000	–	1.057	0.0542	3.707
Prevalent VF	0.866	0.539	–	1.390	0.5511	0.355

BMD bone mineral density, *BAP* bone-specific alkaline phosphatase, *NTX* N-terminal telopeptide of type 1 collagen, *CTX* C-terminal telopeptide of type 1 collagen, *BRM* bone resorption markers, *high BRM* neither urinary NTX nor urinary CTX less than mean + 1.0 SD, *mid BRM* only one of urinary NTX or urinary CTX less than mean + 1.0 SD, *low BRM* both urinary NTX and urinary CTX less than mean + 1.0 SD, *VF* vertebral fracture, *MSC* minimum significant change, *BRMR* bone resorption markers response, *normal BRMR* both urinary NTX and urinary CTX more than MSC, *mid BRMR* only one of urinary NTX or urinary CTX more than MSC, *low BRMR* neither urinary NTX nor urinary CTX more than MSC

significantly decreased BMD response to risedronate. In our study, basal serum 25(OH)D levels were not significantly different between the Rs and IRs; we did not find a statistically significant increase in the IR rate using a 25(OH)D cutoff level of 21 ng/ml as in Mawatari's study, or of 20 ng/ml, as defined by the recently published Japanese criteria for vitamin D deficiency [36]. However, when using a cutoff of 16 ng/mL 25(OH)D, significantly more subjects fell into the IR group. Among the 15 subjects with fracture, 6 (40%) had a serum 25(OH)D level below 16 ng/mL. Differences in the cutoff levels of 25(OH)D associated with an IR between our study and the previous study most likely resulted from different methods of analysis and also from the smaller number of subjects in our study. One of the interesting findings in the present study is that the low 25(OH)D level was associated with IR independent of BTM changes. This suggests that vitamin D deficiency affects bisphosphonate responses not by interfering with bone turnover, for example, via inducing secondary hyperparathyroidism, but by other mechanisms such as negatively influencing bone mineralization. Unlike most [37–40] but not all [41] phase III studies for other bisphosphonates conducted in Japan, subjects enrolled in the

studies included in the present analysis were not supplemented with vitamin D but calcium to keep the consistency with the first risedronate study [42] conducted in Japan as well as the clinical trial for etidronate [43], the active competitor in the first Japanese risedronate study [42]. The lack of vitamin D supplementation in those studies is most likely to have enhanced any deleterious effects of poor basal vitamin D status.

Our finding that relatively low basal BTM (less than the mean + 1.0 SD for Japanese premenopausal women) is associated with IR is in agreement with previous studies of other antiresorptives [44–46]. Higher BTM are generally accepted as a fracture risk [47]. However, higher basal BTM are associated with greater BMD increases with estrogen [45] and calcitonin [44]. In the case of alendronate, higher basal BTM are associated with a better BMD response [46] and greater anti-fracture efficacy [46]. A previous analysis demonstrated that the anti-fracture efficacy of risedronate was not affected by basal urinary deoxypyridinoline (DPD), a bone resorption marker [12]. However, for risedronate, the number needed to treat (NNT) to avoid one VF at 12 months was 15 in the high basal DPD group, which was significantly smaller than 25, the NNT in the low basal DPD group [12]. To the best of our knowledge, no study has reported a relationship between basal BTM and the BMD response to risedronate. However, one study demonstrated that treatment failure according to the IOF definition was associated with higher baseline levels of total alkaline phosphatase activity [7]. Indeed, even in our study subjects, all the BTM values at baseline were higher in the fracture group than in the R or BMD loss groups. As reported by many previous studies, we also found that the IR was strongly associated with a decreased BTM response [48]. When we added BTM changes at 6 months in the multivariate analysis, the relationship with all the baseline BTM disappeared, as reported for procollagen type 1 amino-terminal propeptide (P1NP) in the post hoc analysis in the FACT study [10]. Interestingly, a recent study demonstrated that decreased BTM responses to bisphosphonates are associated with lower basal BTM levels [48]. As discussed earlier, we did not find any differences in the basal vitamin D status between those with normal and blunted BTM responses (data not shown).

The relationship between basal BMD and response to risedronate in the present study is consistent with a previous report [23]. Low BMD is a well-established risk for fracture. However, several studies have indicated that anti-osteoporotic medications are less effective in subjects with a higher bone density. For example, it is well known that alendronate does not have anti-fracture efficacy in non-osteoporotic subjects (femoral neck BMD *T* score > − 2.5 and no prevalent VF) [46]. With risedronate, a previous study reported that 1-year increases in BMD both at the lumbar spine and at the femoral neck were negatively correlated with baseline *T* scores at the respective sites [49]. The post hoc analysis in the FACT study, which compared the effects of once-weekly alendronate and risedronate in the US, demonstrated that BMD non-responders had a significantly higher baseline BMD in the lumbar spine and hip trochanter than responders [10]. Similarly, higher basal BMD was associated with a decreased BMD response to raloxifene in Japanese patients with osteoporosis [50]. Even with teriparatide, which exerts an opposing effect to bisphosphonates or raloxifene on bone turnover, BMD increases were less marked in subjects with higher basal BMD, irrespective of prior bisphosphonate usage [51]. Thus, higher basal BMD appeared to be associated with blunted BMD response to anti-osteoporotic medications across the board, although the exact mechanisms are not known. This may well be in part due to the "regression to the mean" phenomenon, reflecting falsely higher BMD measurement at the baseline in some subjects [16].

Poor adherence has been reported to be associated with the IR to bisphosphonates in many previous studies [3, 32, 35]. It is generally accepted that for osteoporosis medications to effectively increase BMD and to decrease fracture risk, more than 80% adherence is necessary [4]. In our study population, overall adherence was extremely high (96.7%), which reflects the nature of parental studies, i.e., phase III clinical trials. However, we did find that a 1% decrease in adherence, even when adherence was above 80%, was significantly associated with higher rates of IR to risedronate. According to a Japanese study, the average of patient adherence for daily, weekly and monthly bisphosphonates after 1 year was 38.6, 70.6 and 77.7%, respectively [52]. Our results confirm that it is critically important to raise patient adherence towards 100% to ensure the efficacy of bisphosphonates. In the present study, the association of adherence and IR disappeared when BTM changes were incorporated into the multivariate analysis, suggesting that BTM changes were related to adherence as well. Indeed, poor adherence was associated with decreased BAP change at 6 months using Wilcoxon's rank sum test (data not shown), but not with CTX or NTX change, which suggests that BAP monitoring may help in assessing patient adherence as well.

Prior fracture is an established fracture risk and many previous studies have reported an association with IR of the fractures [6, 8, 9]. Because most of the IRs in our study did not have fractures, the existing fracture at baseline was not associated with IR, as reported in a previous study [10]. As reported in some [10], but not all [23] previous studies, age was also not associated with IR. In the present study, we were unable to assess some of the factors that have been reported to be associated with IR in previous studies, including current smoking status [7], poor QOL vitality scores, falls [8] and dementia [9].

The major limitation of this study is the lack of control groups, as the original clinical trials aimed to compare

different dosing regimens of risedronate (daily, weekly, or monthly). Thus, we were unable to compare the relative anti-fracture efficacy among subgroups of our subjects, as all the subjects received risedronate. However, the extremely low rate of VF at 1 year (15/1261 = 1.2%) in our study subjects suggests that risedronate was effective for the prevention of VF in general. Higher rates of VF have been reported in the placebo or non-bisphosphonate competitor groups of other bisphosphonate trials conducted in Japan [20, 40, 41]. A second limitation is that the study duration was relatively short, for only 12 months, which might also be an explanation for the extremely low rate of VF observed in our study. Thirdly, we were unable to analyze hip BMD, which has been shown to correlate better with fracture risk in several previous studies [19, 21].

In conclusion, the present study demonstrates that low serum 25(OH)D, higher BMD at baseline, low BTM levels at baseline or decreased BTM changes at 6 months at either less than 25% or MSC were independently associated with an IR to risedronate in Japanese subjects with osteoporosis. Fractures and BMD loss unsurprisingly make both patients and physicians uncomfortable with the current on-going medications system. The identification of known factors associated with the IR in such patients would assist in the management of the treatment strategy, such as in the correction of vitamin D deficiency and enforcement of drug adherence. This study confirms the clinical importance of assessing the serum 25(OH)D level at baseline and BTM at baseline as well as at an early time point after the initiation of risedronate administration.

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Compliance with ethical standards

Conflict of interest Dr. Ryo Okazaki received grants from Asahi-Kasei Pharma, Astellas Pharma, Chugai Pharmaceutical, Daiichi-Sankyo, EA Pharma, Eisai, Eli Lilly Japan, Ono Pharmaceutical, Taisho-Toyama Pharmaceutical, Takeda Pharmaceutical, and Teijin Pharma, outside of the submitted work. Mr. Ryoichi Muraoka and Mr. Masayuki Maehara received personal fees from EA Pharma Co. Ltd., during the course of the study. Dr. Daisuke Inoue received personal fees from EA Pharma, grants from Asahi-Kasei Pharma, Astellas Pharma, Chugai Pharmaceutical, Daiichi-Sankyo, Eisai, Eli Lilly Japan, Pfizer, Ono Pharmaceutical, Taisho-Toyama Pharmaceutical, Takeda Pharmaceutical, and Teijin Pharma, outside the submitted work.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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