

Higher response with bone mineral density increase with monthly injectable ibandronate 1 mg compared with oral risedronate in the MOVER study

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Abstract We examined response to bone mineral density (BMD) gains in the MOVER study following treatment with intravenous (IV) ibandronate 1 mg/month, and investigated the characteristics of a non-responder group. At 1 year, responder rates for patients with BMD increases >0 % were similar with IV ibandronate 0.5 or 1 mg/month and oral risedronate 2.5 mg/day. However, after 3 years, responder rates with BMD increases ≥ 3 % were highest with ibandronate 1 mg at all bone sites (>80 % at the lumbar spine [L2–L4] and >50 % at all femur sites, which was significantly higher than with risedronate). Non-responders were defined by BMD increases ≤ 3 % at L2–L4 or ≤ 0 % at total hip, and ≤ 50 % reduction in creatinine-corrected urinary collagen type 1 cross-linked C-telopeptide (uCTX) from baseline to 1 year. There were a small number of non-responders in the ibandronate 1 mg group: 3.3 % (10/299) with ≤ 0 % total hip BMD increase and ≤ 50 % uCTX reduction from baseline. These non-responders had lower 25-hydroxyvitamin D (25[OH]D) levels than responders, but no differences in kidney function, L2–L4 BMD or bone turnover marker baseline values. Throughout the study, non-responders failed to show any increases in BMD. Our analysis demonstrates significantly higher responder rates with IV ibandronate 1 mg/month than with risedronate at

3 years. A small number of non-responders in the ibandronate group had lower 25(OH)D baseline levels than responders, suggesting that 25(OH)D levels could be a useful indicator of BMD response to therapy.

Keywords Ibandronate · Intravenous · MOVER study · Osteoporosis · Responders

Introduction

Ibandronate is a nitrogen-containing bisphosphonate that potently inhibits osteoclast-mediated bone resorption. Oral or intravenous (IV) ibandronate, administered intermittently, has been used worldwide for the treatment of osteoporosis. The fracture prevention efficacy of oral ibandronate was first demonstrated in the BONE (oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe) study, which investigated both continuous and intermittent ibandronate dosing [1]. The non-inferiority and superiority of intermittent dosing versus continuous dosing of ibandronate was subsequently shown in the MOBILE (Monthly Oral iBandronate In LadiEs) study [2], which was conducted in accordance with the bridging concept, and in the DIVA (Dosing IntraVenous Administration) study [3,4].

The randomized, double-blind MOVER (MONTHly intraVenous ibandronatE versus daily oral Risedronate) study established the non-inferiority in Japanese patients of monthly IV ibandronate (0.5 or 1 mg) to daily oral risedronate (2.5 mg; licensed dose in Japan) in vertebral fracture incidence [5]. The MOVER study was conducted as a registration trial and led to the approval of monthly IV ibandronate 1 mg for the treatment of osteoporosis in Japan. In an ad hoc analysis of the MOVER study, we

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reported that greater gains in total hip bone mineral density (BMD) after 6 months of treatment were associated with larger reductions in the risk of vertebral fractures after 12, 24, and 36 months [6]. These results suggested that hip BMD values at 6 months may predict future vertebral fracture incidence and provide an opportunity to assess treatment options. The relationship between BMD increases and fracture risk reduction was examined in a meta-analysis of pooled data from four phase III clinical trials of ibandronate. An inverse relationship was observed between increases in lumbar spine BMD and decreases in clinical fracture rate, while increases in total hip BMD were associated with decreases in the rate of non-vertebral fractures [7].

The overall goal of osteoporosis therapy is to reduce the risk of bone fractures. This can be achieved by optimizing treatment adherence, continuously monitoring the efficacy of treatment, and identifying non-responders quickly so that alternative therapies can be given. An increase in BMD is a well-known surrogate marker for predicting the fracture prevention efficacy of a given treatment in clinical practice. In this exploratory analysis of the MOVER study, we evaluated the response to BMD increases following treatment with IV ibandronate 1 mg/month, and investigated the characteristics of a non-responder group.

Materials and methods

Study design and population

The MOVER study design has been published previously [5]. Briefly, this randomized, double-blind, active drug-controlled study compared 0.5 mg/month and 1 mg/month IV ibandronate with 2.5 mg/day oral risedronate in men and women with primary osteoporosis (ClinicalTrials.gov identifier: NCT00447915). The primary study endpoint was to evaluate the non-inferiority of ibandronate to risedronate with regard to the incidence of non-traumatic vertebral fractures over 3 years. In total, 1265 ambulatory men and women aged ≥ 60 years, with fragile bone fracture, BMD of the lumbar spine L2–L4 or proximal femur $< 80\%$ of the young adult mean, and 1–5 vertebral fractures between Th4 and L4 were randomized. Baseline patient characteristics were balanced between the treatment groups (Table 1) [5].

BMD and uCTX assessments

Lumbar spine (L2–L4), femoral neck, trochanter, and total hip BMDs were measured at screening, baseline, and at 6, 12, 24, and 36 months using dual-energy X-ray absorptiometry (DXA) with Hologic and Lunar bone densitometers.

Table 1 Baseline patient characteristics

Treatment	Ibandronate 1 mg/month IV (<i>n</i> = 382)	Risedronate (<i>n</i> = 376)
Women [<i>n</i> (%)]	354 (92.7)	343 (91.2)
Age (years)	72.2 (6.38)	73.0 (6.29)
60–74 years [<i>n</i> (%)]	245 (64.1)	227 (60.4)
≥ 75 years [<i>n</i> (%)]	137 (35.9)	149 (39.6)
Weight (kg)	50.9 (7.36)	51.1 (8.35)
Height (cm)	149.5 (6.56)	149.4 (6.70)
BMD <i>T</i> score		
Lumbar spine (L2–L4)	–2.68 (1.01)	–2.59 (1.06)
Femoral neck	–2.41 (0.80)	–2.53 (0.79)
Total hip	–2.09 (0.86)	–2.18 (0.86)
Prevalent vertebral fractures [<i>n</i> (%)]		
1	184 (48.2)	183 (48.7)
2	106 (27.7)	95 (25.3)
> 2	92 (24.1)	98 (26.1)
uCTX, $\mu\text{g}/\text{mmol CR}$	368.6 (209.9)	373.2 (261.0)
uNTX, nM BCE/mM CR	69.4 (35.42)	68.9 (35.16)
BALP, IU/L	33.9 (13.11)	32.4 (11.96)
25(OH)D (ng/mL)	20.0 (6.69)	19.7 (6.56)

Adapted from [5]

Values are the mean (standard deviation), except where indicated

25(OH)D 25-hydroxyvitamin D, BALP bone-specific alkaline phosphatase, BCE bovine collagen equivalent, BMD bone mineral density, CR creatinine, uCTX creatinine-corrected urinary collagen type 1 cross-linked C-telopeptide, uNTX creatinine-corrected urinary collagen type 1 cross-linked N-telopeptide

The results were analyzed centrally (Synarc, Inc. Portland, OR, USA). Urine samples were collected from patients under fasting conditions prior to study drug administration. Creatinine-corrected urinary collagen type I cross-linked C-telopeptide (uCTX) concentrations were measured centrally at baseline and at 3, 6, 12, 24, and 36 months (Synarc, Inc., Lyon, France).

Non-responders

Non-responders were defined as patients without any fractures within 1 year with both a $\leq 3\%$ change from baseline in L2–L4 BMD at 1 year, and a $\leq 50\%$ change from baseline in uCTX, or patients with both $\leq 0\%$ change from baseline in total hip BMD at 1 year and $\leq 50\%$ change from baseline in uCTX. In this post hoc analysis, *P* values were calculated based on the χ^2 test with Schouten correction and Fisher's exact test, and no multiplicity adjustment was conducted. All statistical analyses were based on the per protocol population and conducted with the use of SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Response according to BMD increases

The proportion of patients with BMD increases $>0\%$ at 1 year was similar in both the ibandronate 1 mg/month and risedronate treatment groups (Fig. 1a). The proportion of responders at the lumbar spine was $>90\%$ with both ibandronate (92.2% [95% confidence interval (CI) 89.0–94.7%]) and risedronate (90.7% [95% CI 87.2–93.4%]), while responder rates at all other bone sites were between 60 and 82%. Significantly higher responder rates were observed at the femoral neck with ibandronate than with risedronate at 1 year: 72.0% (95% CI 67.0–76.6%) versus 59.8% (95% CI 54.5–65.0%), respectively, $P < 0.001$. After 3 years, the proportion of patients with BMD increases $\geq 3\%$ was highest in the ibandronate group at all sites (Fig. 1b). With ibandronate treatment, there was a $>80\%$ responder rate at the lumbar spine, and a $>50\%$ responder rate at all of the femur sites. The patients receiving ibandronate achieved significantly higher responder rates than those receiving risedronate at all of the bone sites (Fig. 1b).

More patients in the ibandronate group than in the risedronate group had a $\geq 6\%$ increase in BMD at the lumbar spine after 3 years of treatment (67.2% [95% CI 62.2–72.0%] vs 56.3% [95% CI 51.1–61.5%]), respectively, $P < 0.01$, as well as a $\geq 3\%$ increase in BMD at the femoral neck (50.7% [95% CI 45.4–56.0%] vs 40.5% [95% CI 35.3–45.8%]), respectively, $P < 0.01$, total hip (55.8%

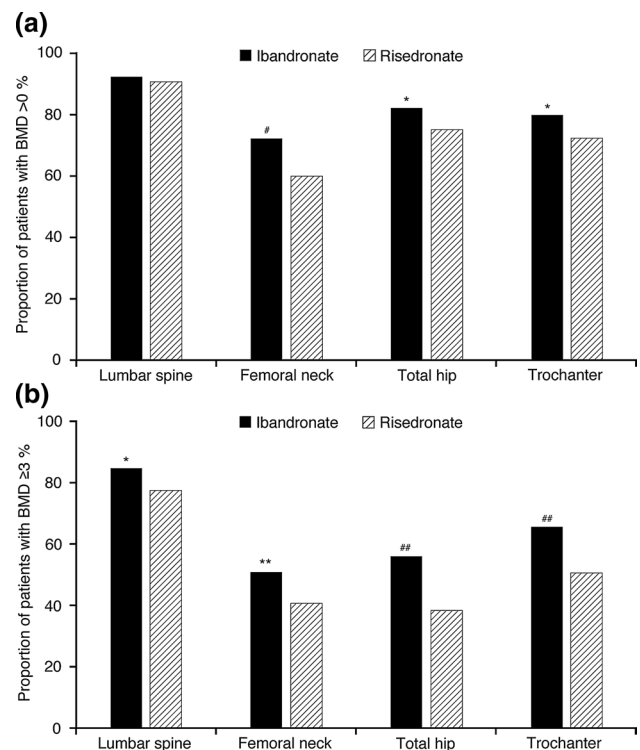


Fig. 1 Responder rates for patients with BMD increases **a** $>0\%$ after 1 year, and **b** $\geq 3\%$ after 3 years; *P* values are for ibandronate versus risedronate: * $P < 0.05$; ** $P < 0.01$; # $P < 0.001$ and ## $P < 0.0001$. No multiplicity adjustment was conducted

[95% CI 50.5–61.1%] vs 38.2% [95% CI 33.1–43.5%], respectively, $P < 0.0001$) and trochanter (65.4% [95% CI 60.2–70.4%] vs 50.4% [95% CI 45.1–55.8%]), respectively, $P < 0.0001$).

Non-responders

Non-responders were identified using scatter plots of the relative change from baseline to 1 year in lumbar spine and total hip BMD and uCTX levels, in patients receiving ibandronate or risedronate (Fig. 2). The proportion of non-responders, defined as those with $\leq 3\%$ increase in L2–L4 BMD and $\leq 50\%$ change in uCTX levels, was 6.1% ($n = 19$) in the ibandronate group and 5.8% ($n = 17$) in the risedronate group. The proportion of non-responders, defined as those with $\leq 0\%$ increase in total hip BMD and $\leq 50\%$ change in uCTX levels, was 3.3% ($n = 10$) in the ibandronate group and 7.1% ($n = 20$) in the risedronate group. Although the number of non-responders with $\leq 0\%$ increase in total hip BMD in the ibandronate group was half that seen in the risedronate group, this difference was not significant.

Table 2 summarizes the baseline characteristics of non-responders and responders characterized by total hip BMD

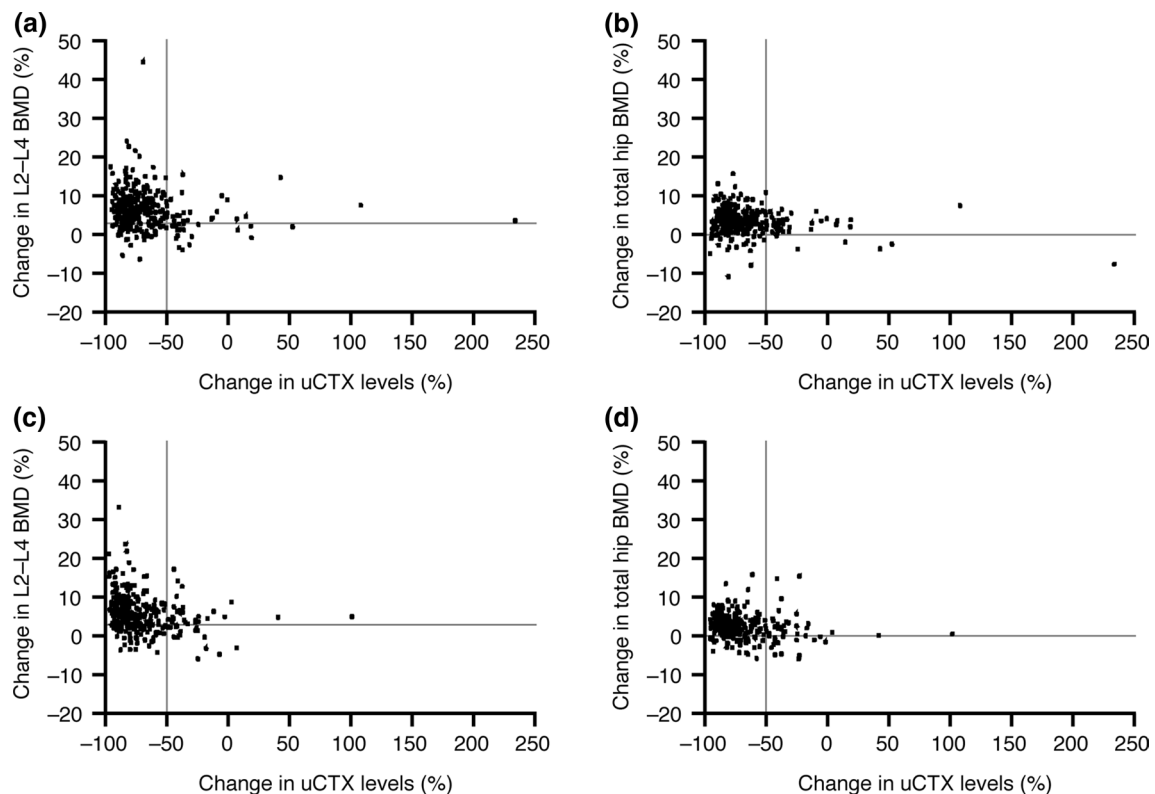


Fig. 2 Scatter plots of relative change from baseline in BMD and uCTX levels to 1 year in patients receiving ibandronate at **a** the lumbar spine and **b** the total hip, and in patients receiving risedronate at **c** the lumbar spine and **d** the total hip

increases and uCTX reductions from baseline at 1 year. Mean 25(OH)D levels in the ibandronate group were significantly lower in non-responders than in responders at baseline, but there were no differences between the two patient groups in terms of renal function, L2–L4 BMD, or bone turnover markers (BTMs). In addition, 25(OH)D levels in non-responders in the ibandronate group did not increase significantly from baseline [16.6 ng/mL (standard deviation [SD] 4.3)] even after 1 year of treatment [19.3 ng/mL (SD 5.1)] with the estimated difference being 2.7 (95 % CI $-1.8 - 7.1$, $P = 0.22$), despite all of the patients having received supplementary calcium 305 mg and vitamin D 200 IU/day during the study (Fig. 3a). In the risedronate group, the 25(OH)D level in non-responders was 19.1 ng/mL (SD 7.0) at baseline, which was not significantly different from the 25(OH)D level in responders after 1 year of treatment, 21.7 ng/mL (SD 5.3), the estimated difference being 2.6 (95 % CI $-1.4 - 6.6$, $P = 0.19$) (Fig. 3b). Changes in total hip BMD were monitored over time in the non-responders (Fig. 4). Mean total hip BMD values of non-responders in the ibandronate group were 0.586 (SD 0.104), 0.571 (SD 0.103), 0.592 (SD 0.113), and 0.577 (SD 0.113) g/cm² at baseline, 1, 2, and 3 years, respectively, and those of non-responders in the risedronate group were similar. Most patients failed to show any increase in BMD after

2 or 3 years of treatment in either the ibandronate or risedronate groups.

The baseline characteristics of non-responders and responders characterized by L2–L4 BMD increases and uCTX reductions from baseline at 1 year were also examined (data not shown). There were 19 (6.1 %) and 17 (5.8 %) L2–L4 non-responders in the ibandronate and risedronate groups, respectively. The characteristics of these non-responders could not be identified. The 25(OH)D level after 1 year of treatment showed wide variation and most patients failed to show any increase in L2–L4 BMD after 2 or 3 years of treatment.

Discussion

The purpose of this exploratory analysis of the MOVES study was to examine the efficacy of IV ibandronate 1 mg/month according to response to therapy in terms of BMD increases, and to clarify the characteristics of patients receiving the drug in order to optimize treatment for osteoporosis.

The proportion of patients who achieved BMD increases from baseline at 1 year was >70 % with ibandronate at all of the sites examined (lumbar spine, femoral neck, total

Table 2 Baseline characteristics of responders and non-responders characterized by BMD increases at the total hip and uCTX reductions

	Ibandronate				Risedronate			
	Responder (n = 289)	Non-responder (n = 10; 3.3 %)	Difference*	95 % CI (P value)	Responder (n = 262)	Non-responder (n = 20; 7.1 %)	Difference*	95 % CI (P value)
Age (years)	71.7 (6.2)	73.1 (6.2)	-1.4	-5.9, 3.1 (0.50)	72.5 (6.2)	73.6 (6.4)	-1.1	-4.1, 2.0 (0.48)
BMI (kg/m ²)	22.7 (2.9)	22.5 (3.4)	0.2	-2.2, 2.6 (0.83)	22.8 (3.1)	22.8 (4.0)	0.1	-1.8, 1.9 (0.95)
L2-L4 BMD T score	-2.66 (1.00)	-3.26 (0.88)	0.60	-0.04, 1.23 (0.06)	-2.58 (1.03)	-2.69 (1.14)	0.12	-0.43, 0.66 (0.66)
Total hip BMD T score	-2.07 (0.87)	-2.52 (0.95)	0.45	-0.23, 1.13 (0.17)	-2.19 (0.82)	-2.25 (0.83)	0.06	-0.34, 0.46 (0.76)
uCTX, µg/mmol CR	358 (197)	439 (278)	-80	-280, 120 (0.39)	378 (280)	311 (176)	68	-20, 156 (0.13)
BALP, IU/L	33.2 (12.8)	36.1 (17.7)	-2.9	-15.6, 9.8 (0.62)	31.7 (10.9)	29.9 (12.8)	1.8	-4.3, 7.9 (0.54)
25(OH)D (ng/mL)	20.4 (6.9)	16.6 (4.3)	3.8	0.7, 6.9 (0.02)	19.9 (6.4)	19.1 (7.0)	0.8	-2.6, 4.2 (0.63)
eGFR (mL/min/1.73 m ²)	77.3 (15.4)	92.2 (23.7)	-14.9	-32.0, 2.1 (0.08)	76.4 (17.6)	81.1 (19.8)	-4.7	-14.1, 4.8 (0.32)
Current smoker [n (%)]	20 (6.9)	3 (30.0)	-23.1	-56.0, 9.1 (0.03)	16 (6.1)	1 (5.0)	1.1	-21.6, 23.9 (1.00)
Prior bisphosphonate use [n (%)]	8 (2.8)	0 (0.0)	2.8	-29.7, 35.4 (1.00)	5 (1.9)	1 (5.0)	-3.1	-25.8, 19.8 (0.36)

*Difference for responder versus non-responder; values are the mean (standard deviation), except where indicated

25(OH)D 25-hydroxyvitamin D, BALP bone-specific alkaline phosphatase, BMD bone mineral density, BMI body mass index, CR creatinine, eGFR estimated glomerular filtration rate, uCTX creatinine-corrected urinary collagen type I cross-linked C-telopeptide

hip, and trochanter), and >60 % with risedronate. Hence, both treatments were sufficiently sensitive within 1 year. After 3 years of treatment, >70 % of patients receiving ibandronate or risedronate achieved a ≥ 3 % increase in lumbar spine BMD from baseline. However, the responder rate at each of the femur sites was ≤ 50 % in the risedronate group at 3 years, while superior response rates were achieved with IV ibandronate.

In the DIVA study, the proportion of patients who achieved BMD increases ≥ 0 % after 1 year of treatment with IV ibandronate 3 mg/3 months and 2 mg/2 months was 92.1 and 92.6 % at the lumbar spine, and 82.3 and 86.4 % for the total hip, respectively [3]. These data are comparable with the responder rates we observed with 1 mg/month ibandronate: 92.2 % at the lumbar spine and 81.9 % for the total hip. These high responder rates at the lumbar spine were also reproduced after 2 years of treatment in the DIVA study: 92.8 % with both 2 mg/2 months and 3 mg/3 months [4]. In addition, the proportion of patients whose lumbar spine BMD increased by ≥ 0 % after 2 years of treatment was 93.5 % following treatment with oral ibandronate 150 mg in the MOBILE study [2]. These comparable gains in BMD in the MOVER, DIVA, and MOBILE studies occurred because each of the ibandronate regimens lies within the high annual cumulative exposure (ACE) category (≥ 10.8 mg) [8]. Meta-analyses of these studies have shown that ibandronate at high ACE affords significant efficacy in terms of both non-vertebral and clinical fracture risk reduction [8–10]. In a retrospective cohort study, patients treated with ibandronate at high ACE had a significantly lower relative risk of vertebral fracture than patients receiving weekly bisphosphonates [11]. Thus, high fracture risk reduction could be achieved through high response rates to ibandronate administered at high ACE (i.e., IV ibandronate 1 mg/month in the present study), with BMD gains at all sites.

Bisphosphonates with low mineral binding affinity, such as ibandronate or risedronate, can be efficiently delivered to the cortical bone area [6]. However, in a pooled analysis of three pivotal risedronate fracture trials, changes in lumbar spine BMD contributed only 18 % (95 % CI 10–26 %) of the drug's vertebral fracture efficacy [12]. Furthermore, ibandronate was administered by the IV route, hence its bioavailability was 100 %. These findings may explain our observation of greater BMD gains with ibandronate than risedronate at the femur sites.

In defining non-responders in the MOVER study, we examined both BMD increases and BTM responses. The study was managed as a registration trial and compliance rates in the modified intent-to-treat population were >96 % for IV ibandronate and >93 % for oral risedronate. These high adherence rates resulted in a low proportion of non-responders (<10 % in both treatment groups); the proportion

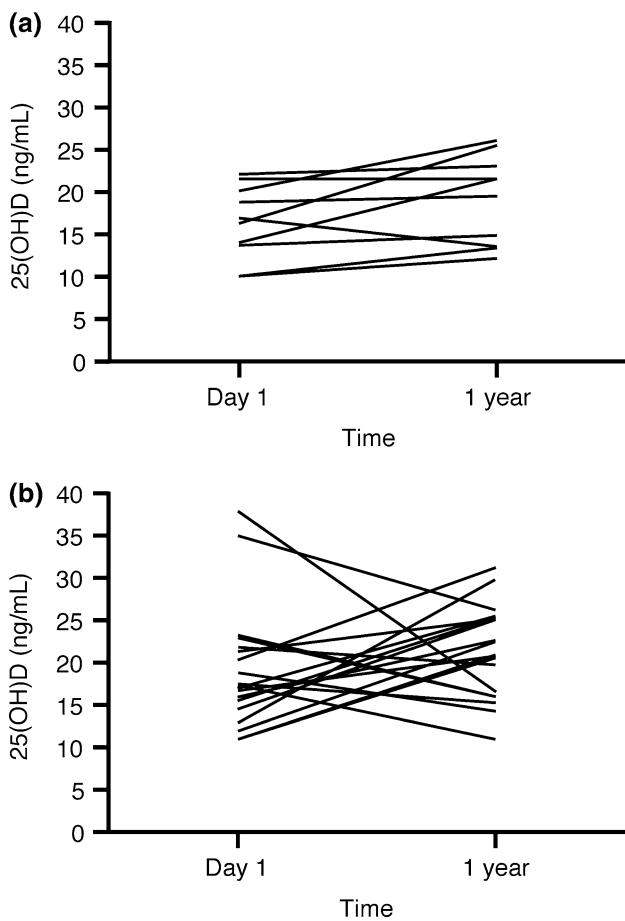


Fig. 3 Change in 25(OH)D levels from baseline to 1 year at the total hip in non-responders receiving **a** ibandronate ($n = 10$), or **b** risedronate ($n = 20$)

of non-responders in the ibandronate group was half that seen in the risedronate group. We were unable to identify any specific baseline patient or disease characteristics that characterized the non-responders. As previously reported [13], non-responders tended to have lower 25(OH)D levels than responders, but no other differences were observed between the two patient groups. Baseline 25(OH)D levels were 20.0 ng/mL (SD 6.69) in the ibandronate group and 19.7 ng/mL (SD 6.56) in the risedronate group. In the primary analysis of MOVER, after 3 years, 25(OH)D levels increased to 26.6 ng/mL (SD 6.71) and 26.9 ng/mL (SD 6.07), respectively, and BMD increases at the lumbar spine were 9.0 and 7.6 %, respectively [5]. These data suggest that the rise in 25(OH)D levels contributes to BMD increases, but the difference in the magnitude of the BMD increase between ibandronate and risedronate cannot be explained. Conversely, in this current analysis, 25(OH)D levels in non-responders to ibandronate remained below 20 ng/mL even after supplementation for 1 year. The lower baseline 25(OH)D value appeared to be specific for non-responders in the ibandronate

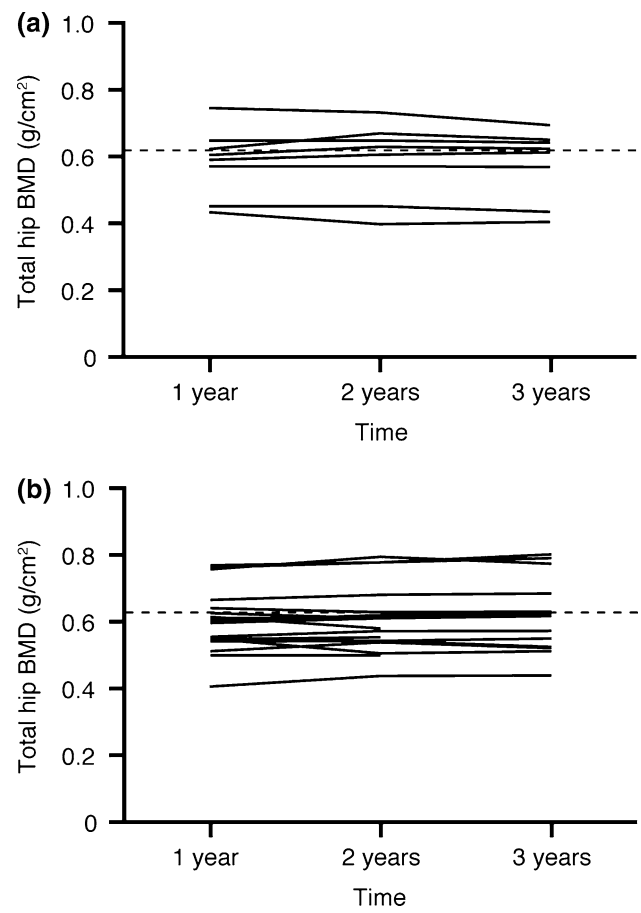


Fig. 4 Total hip BMD increases in non-responders receiving **a** ibandronate ($n = 10$), or **b** risedronate ($n = 20$) over 1–3 years; the dotted line indicates -2.5 standard deviations of the T score

group. Ibandronate induces a higher response rate than risedronate (Fig. 1), and the proportion of non-responders in the ibandronate group was relatively small (Table 2). We anticipate that achieving sufficient vitamin D levels in these patients would enable efficacious bolus administration of monthly ibandronate. Although 25(OH)D measurement is not reimbursed in Japan, it is believed that supplementation with an appropriate dose of vitamin D increases response rates to bisphosphonate therapy in clinical practice [13].

It is important for physicians to avoid non-response to first-line bisphosphonate therapy for patients with osteoporosis. They should strive to inform patients of the effectiveness of the drugs, highlight the importance of compliance, and expect the regimen to improve outcomes. If IV ibandronate is reliably administered, most patients are expected to achieve an increase in BMD at all sites. Although it will be difficult to predict non-responders to therapy by reviewing their baseline characteristics, 25(OH)D levels may be useful in this regard. It is also important to measure changes in BMD or BTMs for the purpose of motivating

patients and improving adherence, which will ultimately contribute to fracture risk reduction.

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Compliance with Ethical Standards

Conflict of interest Tetsuo Nakano has received consulting fees from Asahi Kasei Pharma Corp., Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Inc., and Teijin Pharma Ltd. Masao Yamamoto, Junko Hashimoto, Masato Tobinai, and Seitaro Yoshida are employees of Chugai Pharmaceutical Co. Ltd. Toshitara Nakamura has received research grants and/or consulting fees from Asahi Kasei Pharma Corp., Astellas Pharma Inc., Banyu Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Inc., Eisai Co. Ltd., Eli Lilly Japan K.K., Ono Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., and Teijin Pharma Ltd., and belongs to the Japan Ministry of Health, Welfare and Labor as a councillor for hospital administration and social medical insurance.

References

- Chesnut CH III, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, Felsenberg D, Huss H, Gilbride J, Schimmer RC, Delmas PD (2004) Oral ibandronate osteoporosis vertebral fracture trial in North America and Europe (BONE) effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Min Res* 19:1241–1249
- Reginster JY, Adami S, Lakatos P, Greenwald M, Stepan JJ, Silverman SL, Christiansen C, Rowell L, Mairon N, Bonvoisin B, Drezner MK, Emkey R, Felsenberg D, Cooper C, Delmas PD, Miller PD (2006) Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. *Ann Rheum Dis* 65:654–661
- Delmas PD, Adami S, Strugala C, Stakkestad JA, Reginster JY, Felsenberg D, Christiansen C, Civitelli R, Drezner MK, Recker RR, Bolognese M, Hughes C, Masanauskaite D, Ward P, Sambrook P, Reid DM (2006) Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study. *Arthritis Rheum* 54:1838–1846
- Eisman JA, Civitelli R, Adami S, Czerwinski E, Recknor C, Prince R, Reginster JY, Zaidi M, Felsenberg D, Hughes C, Mairon N, Masanauskaite D, Reid DM, Delmas PD, Recker RR (2008) Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. *J Rheumatol* 35:488–497
- Nakamura T, Nakano T, Ito M, Hagino H, Hashimoto J, Tobinai M, Mizunuma H, MOVER Study Group (2013) Clinical efficacy on fracture risk and safety of 0.5 mg or 1 mg/month intravenous ibandronate versus 2.5 mg/day oral risedronate in patients with primary osteoporosis. *Calcif Tissue Int* 93:137–146
- Hagino H, Yoshida S, Hashimoto J, Matsunaga M, Tobinai M, Nakamura T (2014) Increased bone mineral density with monthly intravenous ibandronate contributes to fracture risk reduction in patients with primary osteoporosis: three-year analysis of the MOVER study. *Calcif Tissue Int* 95:557–563
- Sebba AI, Emkey RD, Kohles JD, Sambrook PN (2009) Ibandronate dose response is associated with increases in bone mineral density and reductions in clinical fractures: results of a meta-analysis. *Bone* 44:423–427
- Harris ST, Blumentals WA, Miller PD (2008) Ibandronate and the risk of non-vertebral and clinical fractures in women with postmenopausal osteoporosis: results of a meta-analysis of phase III studies. *Curr Med Res Opin* 24:237–245
- Cranney A, Wells GA, Yetisir E, Adami S, Cooper C, Delmas PD, Miller PD, Papapoulos S, Reginster JY, Sambrook PN, Silverman S, Siris E, Adachi JD (2009) Ibandronate for the prevention of nonvertebral fractures: a pooled analysis of individual patient data. *Osteoporos Int* 20:291–297
- Miller PD, Recker RR, Harris S, Silverman S, Felsenberg D, Reginster J, Day DM, Barr C, Masanauskaite D (2014) Long-term fracture rates seen with continued ibandronate treatment: pooled analysis of DIVA and MOBILE long-term extension studies. *Osteoporos Int* 25:349–357
- Harris ST, Reginster JY, Harley C, Blumentals WA, Poston SA, Barr CE, Silverman SL (2009) Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: the eValuation of Ibandronate Efficacy (VIBE) database fracture study. *Bone* 44:758–765
- Watts NB, Cooper C, Lindsay R, Eastell R, Manhart MD, Barton IP, van Staa TP, Adachi JD (2004) Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. *J Clin Densitom* 7:255–261
- Carmel AS, Shieh A, Bang H, Bockman RS (2012) The 25(OH) D level needed to maintain a favorable bisphosphonate response is ≥ 33 ng/ml. *Osteoporos Int* 23:2479–2487