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ORIGINAL ARTICLE

Effectiveness of monthly intravenous ibandronate on the low responders to oral bisphosphonate: the MOVEMENT study

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Abstract

The MOVEMENT study was designed to assess the effectiveness of monthly intravenous ibandronate on bone mineral density (BMD) in daily clinical practice in Japanese patients with primary osteoporosis whose lumbar spine BMD did not increase despite oral bisphosphonate therapy. This study was a multicenter, prospective, interventional study (52 sites; August 2015 to March 2018). Patients aged ≥ 50 years with primary osteoporosis, evaluated as low responders to oral bisphosphonate treatment for 1–3 years, continued on their existing oral bisphosphonate or switched to monthly intravenous ibandronate (1 mg) for 12 months. The primary endpoint was change in lumbar spine BMD from baseline to 12 months in the intravenous ibandronate group (IV IBN). A total of 240 and 141 patients were enrolled in the IV IBN and oral bisphosphonate groups (OBP), respectively. At 12 months, a significant increase in mean percent change from baseline in lumbar spine BMD was observed in the IV IBN (2.70%). This change was also significant at 6 months (1.92%). Similarly, the change in total hip BMD showed a significant increase at 12 months (0.78%). In the IV IBN, the responder rate, percentage of patient whose change from baseline of lumbar spine BMD has greater than 0%, for lumbar spine BMD was high at both 6 (72.3%, 141/195 patients) and 12 (78.0%, 145/186 patients) months. No new safety concerns were observed in either treatment group. Treatment with intravenous ibandronate significantly increased lumbar spine BMD without any new safety concerns in Japanese patients with osteoporosis who showed low response to existing oral bisphosphonates.

Keywords Osteoporosis · Monthly intravenous ibandronate · Low responder · Oral bisphosphonate · MOVEMENT study

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Introduction

Bisphosphonates are commonly used as first-line treatment in osteoporosis for prevention of vertebral, non-vertebral, and hip fractures [1, 2]. Globally, guidelines recommend a wide range of bisphosphonates, and no distinction is made between their use in prevention or treatment of such fractures [3–6].

In general, oral bisphosphonates are known to have low bioavailability (0.63–1.8%), which is further reduced in the presence of food [7, 8]. Another challenge associated with bisphosphonates is that of low responders, i.e., patients who show low increase in lumbar spine bone mineral density (BMD) after a period of treatment [9, 10].

To overcome these challenges, efforts are being made to improve bisphosphonate formulations, which are now available as daily, weekly, monthly, and intermittent oral regimens, as well as monthly, quarterly, and yearly intravenous (IV) regimens. In Japan, bisphosphonates such as ibandronate,

alendronate, risedronate, minodronate, and zoledronate are available in a variety of dosages and regimens [11].

Among these, monthly intravenous ibandronate (Bonviva®) 1 mg injection and monthly oral ibandronate 100 mg tablet are approved in Japan for the treatment of osteoporosis [12]. The MOVER study demonstrated non-inferiority of monthly IV ibandronate (0.5 mg/1 mg) versus daily oral risedronate (2.5 mg) over 3 years of treatment for first new vertebral fracture in Japanese patients with primary osteoporosis. Monthly IV ibandronate was also non-inferior to daily oral risedronate in reducing the incidence of vertebral fracture [13]. Thereafter, the 3-year analysis of the MOVER study also showed a significant increase in mean hip BMD with IV ibandronate 1 mg in patients with or without vertebral fractures [14]. Furthermore, a large-scale, multicenter, prospective, observational, post-marketing study examined the safety and effectiveness of monthly IV ibandronate 1 mg for patients with osteoporosis [15]. No new safety concerns were identified. Significant BMD gains at lumbar spine, total hip, and femoral neck were observed. This study showed the safety and effectiveness of monthly IV ibandronate for patients with osteoporosis in routine clinical practice [15]. Overall, these studies have demonstrated significant increases in lumbar spine BMD, total hip BMD, and fracture prevention with oral or IV ibandronate in patients with osteoporosis; however, treatment options for low responders to oral bisphosphonates are limited and are being explored [16].

This study was conducted to assess the effect of IV ibandronate on BMD in daily clinical practice in Japanese patients with primary osteoporosis whose lumbar spine BMD did not increase despite oral bisphosphonate therapy for 1–3 years.

Materials and methods

Study design

The MOVEMENT (the effect of MOnthly ibandronate iV injected on the low-responders to pre-Existing oral bp treatMEnt for the osteoporosis patieNTs) study was a multicenter, prospective, interventional study conducted at 52 sites across Japan between August 2015 and March 2018. The present study is registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000017819). During the registration period of 18 months (August 2015 to March 2017), patients who were evaluated as low responders to oral bisphosphonates (alendronate, minodronate, or risedronate) were enrolled. Low responders were defined as those who showed a rate of change of $\leq 0\%$ in the past two assessments of lumbar spine BMD before enrollment, despite high compliance to oral bisphosphonate treatment ($\geq 75\%$) in the past year. These patients continued on their existing oral bisphosphonates or switched to monthly IV ibandronate (1 mg), to any of the other two oral bisphosphonates, or to an amended dose of existing oral bisphosphonate. Change in the dosing interval was also permitted for oral bisphosphonates. The intake of calcium and vitamin D was permitted, but the change of dosage of vitamin D was not permitted. The intervention was selected at the time of enrollment based on discussion between the investigator and the patient. Patients were followed up for 12 months of study treatment.

The protocol was reviewed and approved by the Institutional Review Boards at all the participating study sites. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional review boards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All individuals provided written informed consent before enrollment in this study.

Patients

Patients of either sex, aged ≥ 50 years, with a diagnosis of primary osteoporosis as per the 2012 revised diagnostic criteria for primary osteoporosis from The Japanese Society for Bone and Mineral Research [17], no history of IV ibandronate administration, a decreasing trend in lumbar spine BMD [$\leq 0\%$ change in lumbar spine BMD between past two assessments (interval of 6–13 months) before enrollment], history of oral bisphosphonate use for 1–3 years, and oral bisphosphonate compliance rate of $\geq 75\%$ as questionnaire for patient by physician in the past year were enrolled.

Key exclusion criteria included secondary osteoporosis, lumbar spine BMD T-score < -4, ≥ 2 prevalent fractures in L1–L4, and findings that may affect dual-energy X-ray absorptiometry (DXA) measurements. Patients having a history of use of selective estrogen receptor modulator (SERM), sex hormone (excluding topical medications such as vaginal suppository), adrenocortical hormone (except topical medications), or insulin within 8 weeks before enrollment, and those having a history of use of parathyroid hormone (PTH), antibody to receptor activator of NF-κB ligand (RANKL), anti-sclerostin antibody, cathepsin K inhibitors, zoledronate, or IV alendronate within 12 months before enrollment were also excluded.

Treatment

Patients in the IV ibandronate group (IV IBN) received ibandronate (Bonviva® IV Injection 1 mg Syringe, Chugai Pharmaceutical Co., Ltd.) once monthly according to the prescribing information. Patients in the oral bisphosphonate group (OBP) received alendronate [daily (5 mg) or

weekly (35 mg) tablets or weekly jelly formulation (35 mg)], minodronate [daily (1 mg) or monthly (50 mg) tablets], or risedronate [daily (2.5 mg), weekly (17.5 mg), or monthly (75 mg) tablets] according to the prescribing information. Administration of SERM, PTH, anti-RANKL antibody, anti-sclerostin antibody, cathepsin K inhibitors, zoledronate, IV alendronate, sex hormone (excluding topical medications such as vaginal suppository), systemic adrenal corticosteroid, or insulin was prohibited during the study.

Endpoints

The primary endpoint was the change in lumbar spine (L1–L4) BMD from baseline to 12 months in the IV IBN. Secondary endpoints were change from baseline in lumbar spine BMD (6 months) and total hip BMD (6 and 12 months); responder rate (percentage of patients with an increase in lumbar spine BMD from baseline, 6 months, and 12 months, has greater than 0%); change from baseline in bone turnover markers [BTMs; serum C-terminal telopeptide of type 1 collagen (sCTX), tartrate-resistant acid phosphatase isoform 5b (TRACP-5b), and procollagen type 1 amino-terminal pro-peptide (P1NP); 3 and 12 months]; and hip structure analysis (HSA) index [cross-sectional moment of inertia (CSMI), section modulus (SM), and buckling ratio (BR) in the narrow neck, intertrochanter, and femoral shaft; 6 and 12 months] in the IV IBN.

A matching analysis using propensity score matching (PSM) was also performed between the IV IBN and OBP as part of the secondary endpoint analyses. Changes from baseline in lumbar spine (L1–L4) and total hip BMD (6 and 12 months), BTMs (3 and 12 months), and HSA index (6 and 12 months) and incidence of clinical fracture were compared between the groups.

Safety endpoints were incidence of adverse events (AEs) and calcium (Ca)-related laboratory tests. AEs of special interest were selected as per the system organ classes and preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) in consideration of common safety concerns associated with osteoporosis pharmacotherapy [18, 19]. The onset of acute-phase reactions (APRs, e.g., influenza-like illness, pyrexia, arthralgia, joint injury, and dizziness) that occurred within the first 3 days of initiating the study drug was assessed retrospectively.

Assessments

Lumbar spine (L1–L4) and total hip BMD was measured by the DXA system (Hologic, Inc.) at baseline, 6, and 12 months and assessed by an independent, blinded central review. Thoracic and lumbar spine X-ray was performed at baseline, 6, and 12 months for clinical fracture assessment as reported by physicians. Drug compliance was assessed at 3, 6, and 12 months of treatment, and a patient diary was used for recording assessments. In the IV IBN, patients were prescribed drugs in hospital. Blood/serum was collected for Ca-related tests (serum creatinine, calcium, phosphorus, and albumin) performed at baseline, 3, and 12 months. Blood/serum was collected for Ca-regulating hormones (25-hydroxyvitamin D and intact PTH at baseline) and BTMs (sCTX, TRACP-5b, and P1NP; baseline, 3, and 12 months) and were centrally measured at LSI Medience Corporation (Tokyo, Japan). AEs were collected throughout the study period and coded using MedDRA version 21.0.

Statistical analysis

Based on previous study results [20, 21], a sample size of 400 was set from a hypothesis that lumbar spine BMD increases by 1% from baseline to 12 months after switching to IV ibandronate. For the IV IBN, a sample size of 199 was calculated to detect a 1% increase with a power of 80%, assuming a standard deviation (SD) of 5%. As for the OBP, the sample size of 120 was calculated to detect at least 0.5% difference between the IV IBN and OBP with a probability of 80%. Considering a dropout rate of 20%, the final sample size was set to 250 and 150 for the IV IBN and OBP, respectively. Effectiveness was assessed in the full analysis set (FAS), which comprised all enrolled patients excluding those who were outside of the study target disease, did not receive the study drug, or had no available effectiveness data. The safety analysis set consisted of patients who received at least one dose of the study drug.

For the PSM in the FAS, each patient in the IV IBN was matched with one patient in the OBP who satisfied clinically relevant matching criteria and had the least difference. Propensity score (PS) was estimated by a logistic regression model using matching factors that may have affected the outcome as the covariate. Statistical significance was evaluated at a two-sided significance level of 5%. A paired *t* test was performed for the change from baseline in lumbar spine and total hip BMD, BTMs, and HSA index in the IV IBN. In the matching analysis, background factors in the matched cohort were compared between the IV IBN and OBP using the paired *t* test, Wilcoxon rank-sum test, and Chi-square test. Change from baseline in lumbar spine and total hip BMD, BTMs, and HSA index was compared using the paired *t* test. The incidence of clinical fracture was compared using the McNemar test. Mean percent change from baseline (95% confidence interval [CI]) at 12 months in lumbar spine BMD was assessed for select predefined subgroups and post hoc subgroups based on patient characteristics. All statistical analyses were performed using the SAS software (SAS for Windows Release version 9.4, SAS Institute Inc.).

Results

Baseline demographics and characteristics

A total of 240 and 141 patients were enrolled in the IV IBN and OBP, respectively (Fig. 1). Among them, 209 (87.1%) and 125 (88.7%) patients completed the 12-month follow-up period in the IV IBN and OBP, respectively. A total of 31 and 16 patients discontinued, with the most common reason being patient's choice (19 and eight patients) followed by AEs (seven and six patients) in the IV IBN and OBP, respectively.

Overall, baseline patient characteristics were comparable between the groups (Table 1). The mean ± SD age was 74.8 ± 7.6 years and 74.3 ± 7.6 years in the IV IBN and OBP, respectively, with the vast majority of patients being women. Prevalent fracture was reported in almost half of the patients in both treatment groups. Oral minodronate, alendronate, and risedronate had been prescribed to 117 (52.5%), 40 (17.9%), and 65 (29.1%) patients in IV IBN and 85 (62.5%), 31 (22.8%), and 20 (14.7%) patients in OBP, respectively. The intake of calcium and vitamin D was permitted, but the change of dosage of vitamin D was not permitted. Most patients were concomitant with active vitamin D3 agents (133 and 76 patients, IV IBN and OBP). The serum level of 25 (OH) VD_3 at baseline was 15.92 ± 6.17 of the IV IBN and 15.86 ± 6.42 ng/mL of OBP, respectively.

Study treatment and drug compliance rate

In the OBP, 140 patients continued their existing oral bisphosphonate after enrollment, while one patient switched from monthly minodronate 50 mg to daily minodronate 1 mg. At 12 months, treatment compliance rate was 100% in 202 patients (95.7%) in the IV IBN and 115 patients (92.0%) in the OBP. A compliance rate of < 75% was observed only in two (0.9%) and two (1.6%) patients in the IV IBN and OBP, respectively. These patients were included in the FAS.

Effectiveness

At 12 months, a significant increase in mean percent change from baseline in the lumbar spine BMD was observed in the IV IBN (primary endpoint: 2.70% [95% CI 2.22–3.18], $p < 0.0001$; Fig. 2a). This change was also significant at 6 months (1.92% [95% CI 1.45–2.40], $p < 0.0001$; Fig. 2a). Similarly, the mean percent change in total hip BMD in the IV IBN also significantly increased from baseline to 6 months (0.76% [95% CI 0.43–1.08], $p < 0.0001$) and 12 months (0.78% [95% CI 0.41–1.15], $p < 0.0001$) (Fig. 2b). The responder rate was high at both 6 months (72.3%, 141/195 patients) and 12 months (78.0%, 145/186 patients) (Fig. 2c).

A significant increase in mean percent change from baseline was observed for all BTMs in the IV IBN at 12 months [FAS: sCTX, 15.9% ($p < 0.0001$); TRACP-5b, 7.2% ($p < 0.0001$); P1NP, 8.5% ($p = 0.0019$)].

In comparison, an additional analysis of the OBP showed a numerical increase in mean percent change from baseline in both lumbar spine BMD at 6 months (1.98% [95% CI 1.45–2.51]) and 12 months (2.25% [95% CI 1.63–2.86]) and total hip BMD at 6 months (0.59% [95% CI 0.09–1.08]) and 12 months (0.61% [95% CI 0.03–1.19]). The responder rate in the OBP was 71.7% (86/120 patients) and 73.9% (85/115 patients) at 6 and 12 months, respectively.

At 12 months, a significant improvement from baseline was observed in the HSA indices in the IV IBN at the narrow neck (CSMI: 0.020 cm^4, $p = 0.0437$), intertrochanter region (BR: − 0.119, $p = 0.0025$), and femoral shaft

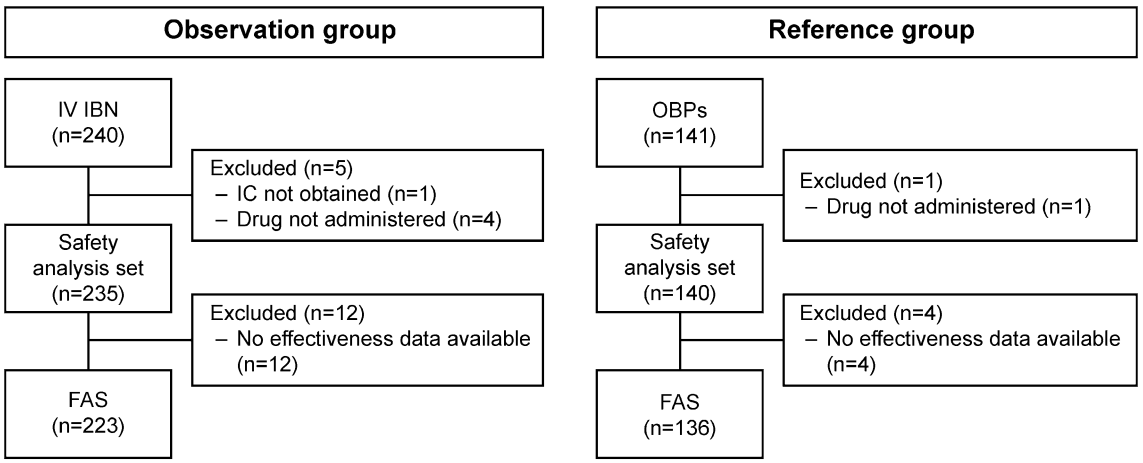

Fig. 1 Patient flow. *FAS* full analysis set, *IC* informed consent, *IV IBN* intravenous ibandronate, *OBPs* oral bisphosphonates

Table 1 Baseline patient demographics and characteristics (FAS)

Characteristics	IV IBN (n=223)	OBP (n=136)
Sex (female), n (%)	213 (95.5)	132 (97.1)
Age (years), mean ± SD	74.8 ± 7.6	74.3 ± 7.6
≥ 65 years, n (%)	200 (89.7)	123 (90.4)
Height (cm), mean ± SD	150.3 ± 6.1	150.6 ± 7.0
Body weight (kg), mean ± SD	50.0 ± 7.4	50.6 ± 8.6
BMI (kg/m^2), mean ± SD	22.1 ± 3.1	22.4 ± 3.7
Menopause[a], n (%)	213 (95.5)	132 (97.1)
Prevalent fracture, n (%)	111 (49.8)	75 (55.1)
Current smoking, n (%)	8 (3.6)	10 (7.4)
Alcohol intake (≥ 3 units/day)	18 (8.1)	12 (8.8)
Current BP agents, n (%)		
Alendronate	40 (17.9)	31 (22.8)
Minodronate	117 (52.5)	85 (62.5)
Risedronate	65 (29.1)	20 (14.7)
Others	1 (0.4)	0 (0.0)
Concomitant medication, n (%)	138 (61.9)	79 (58.1)
Active vitamin D_3 agents, n	133	76
Lumbar spine BMD (L1–L4, g/cm^2), mean ± SD	0.714 ± 0.111	0.733 ± 0.121
Total hip BMD (g/cm^2), mean ± SD	0.682 ± 0.084	0.686 ± 0.104
sCTX (ng/mL), mean ± SD	0.153 ± 0.096	0.149 ± 0.108
TRACP-5b (mU/dL), mean ± SD	267.6 ± 116.2	262.2 ± 119.1
P1NP (μg/L), mean ± SD	21.94 ± 12.23	21.43 ± 11.56
25-OH-VD_3 (ng/mL), mean ± SD	15.92 ± 6.17	15.86 ± 6.42
iPTH (pg/mL), mean ± SD	38.9 ± 15.1	41.3 ± 25.7

Data are presented as n (%) unless otherwise specified

25-OH-VD$_3$ 25-hydroxyvitamin D_3, *BMD* bone mineral density, *BMI* body mass index, *BP* bisphosphonate, *FAS* full analysis set, *iPTH* intact-parathyroid hormone, *IV IBN* intravenous ibandronate group, *OBP* oral bisphosphonate group, *P1NP* procollagen type 1 amino-terminal pro-peptide, *sCTX* serum C-telopeptide cross-link of type 1 collagen, *SD* standard deviation, *TRACP-5b* tartrate-resistant acid phosphatase isoform 5b

[a]One patient in the IV IBN and two patients in the OBP had unknown status for menopause

(CSMI: 0.021 cm^4, p=0.0125; SM: 0.011 cm^3, p=0.0246) (data are supplied in Supplementary Table S1).

Mean percent changes from baseline to 12 months in lumbar spine BMD regarding background of patients are shown in Fig. 3. Consistently, the results showed that the lumbar spine BMD in both treatment groups has increased in all factors. In particular, the analysis of the IV IBN showed that the mean percent change from baseline to 12 months in lumbar spine BMD was numerically higher among those switched from risedronate (4.2% [95% CI 3.2–5.3]), compared to those switched from alendronate (2.0% [95% CI 0.7–3.3]) or minodronate (2.2% [95% CI 1.6–2.8]) (Fig. 3).

Matching analysis

A total of 108 patients each from the IV IBN and OBP were included in the matched cohort. All patient background characteristics were similar in the matched cohort except for serum creatinine, estimated glomerular filtration rate (eGFR), and lumbar spine BMD (Table 2). No statistically significant difference was observed between the two treatment groups for all parameters assessed in the PSM analysis (Table 3). However, the mean percent change of P1NP and TRACP-5b in the IV IBN was numerically lower compared to that in the OBP, and that of the sCTX in the IV IBN was numerically higher compared with that in the OBP.

Incidence of clinical fracture was not significantly different between both groups (2.8% in IV IBN vs 2.8% in OBP, p=1.0000). The mean change of HSA indices also was not significantly different (improvement) between the IV IBN and OBP group in the PSM analysis (data are supplied in Supplementary Table S2).

Safety

The most frequently reported AE was injury, poisoning and procedural complications (13.2%), followed by musculoskeletal and connective tissue disorders (11.5%), infections and infestations (9.8%), and skin and subcutaneous tissue disorders (3.4%) in the IV IBN. The most common AE in the OBP was infections and infestations (10.0%), followed by musculoskeletal and connective tissue disorders (7.1%) and injury, poisoning and procedural complications (3.6%) (Table 4). Serious adverse drug reactions (ADRs) were reported, one event each (one patient each) of pancreatic cyst and dizziness in the IV IBN. Three AEs in two patients in the IV IBN (arthralgia, joint injury, and dizziness) were identified as APRs, but they were all mild in severity and had no causal relationship, except dizziness.

The mean serum creatinine, calcium, phosphorus, and albumin at baseline and 3 and 12 months after administration was within the range of 0.670–0.675 mg/dL, 9.32–9.36 mg/dL, 3.35–3.39 mg/dL, and 4.18–4.23 g/dL, respectively, in IV IBN and 0.687–0.709 mg/dL, 9.32–9.39 mg/dL, 3.35–3.39 mg/dL, and 4.21–4.26 g/dL, respectively, in OBP. The mean eGFR was 68.39–68.57 mL/min/1.73 m^2 in IV IBN and 67.56–65.83 mL/min/1.73 m^2 in the OBP.

Discussion

We evaluated the effectiveness of IV ibandronate on BMD gains in patients with primary osteoporosis with no increase in lumbar spine BMD, despite oral bisphosphonate therapy for 1–3 years. Low responders who switched from existing oral bisphosphonates to IV ibandronate showed a significant

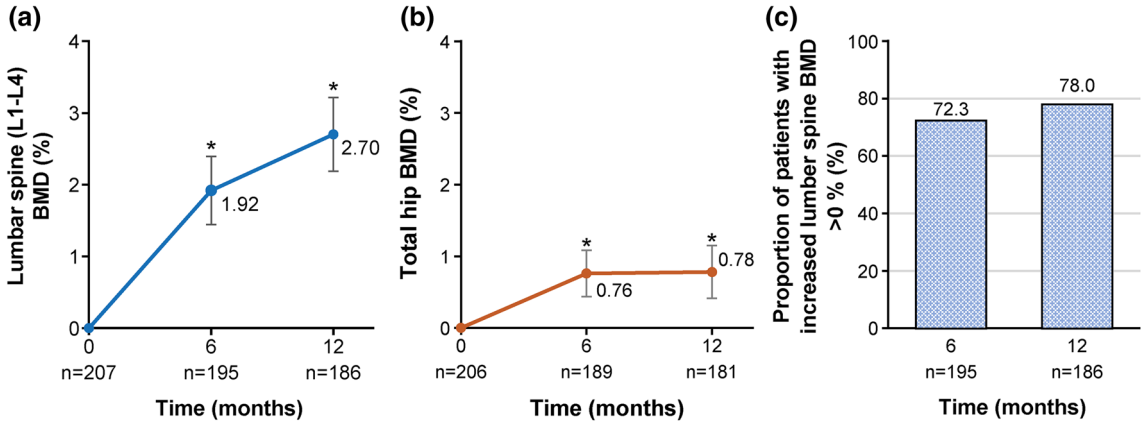

Fig. 2 Mean percent change (95% CI) from baseline to 12 months in, **a** lumbar spine (L1–L4) and **b** total hip BMD, **c** responder rate in the IV IBN (FAS). *BMD* bone mineral density, *CI* confidence interval, *FAS* full analysis set, *IV IBN* intravenous ibandronate group. **p* value < 0.0001

increase in lumbar spine (L1–L4) BMD (2.70%, $p < 0.0001$) from baseline to 12 months and the responder rate at 12 months was 78.0%, with no new safety concerns and no apparent increase in the nature or severity of ADRs.

There have been efforts to improve bisphosphonate formulations to overcome the challenges associated with their use; nonetheless, the incidence of low responders to oral bisphosphonates remains a concern. Change in delivery route has been identified as likely to have a greater impact on BMD in low responders [22]. To our knowledge, this is the first study to assess the effect of IV ibandronate in Japanese patients with primary osteoporosis who showed low response to their existing oral bisphosphonate. The mean lumbar spine BMD significantly increased from baseline in the IV IBN as early as 6 months (1.92%) and continued to increase as measured at 12 months (2.70%). The mean total hip BMD in the IV IBN also significantly increased from baseline to 6 months (0.76%) and 12 months (0.78%). This was supported by a significant increase in many HSA indices at 12 months. The overall responder rate was > 70% at both 6 and 12 months. An increase from baseline was observed for all BTMs, indicating high bone turnover. No excessive suppression was observed in TRACP-5b. The results for BMD in the matched cohort analysis, although numerically higher, did not differ notably between the IV IBN and OBP.

Reasons for low response to oral bisphosphonates are multifactorial and include poor compliance and persistence, inadequate intake of calcium and vitamin D, malabsorption, a comorbid disease or disorder with adverse skeletal effects, metabolic factors, wrong dose, wrong dosing interval, and/or lack of efficacy [23]. Furthermore, the definition of low responders to bisphosphonates is inconsistent among studies and is likely to vary with the choice of bisphosphonate. The analysis of the MOVER study defined low responders as patients with BMD increases ≤ 3% at L2–L4 or ≤ 0% at total hip and ≤ 50% reduction in creatinine-corrected urinary CTX from baseline to 1 year [24]. In the current study, low responders had a rate of change of ≤ 0% in the past two assessments of lumbar spine BMD despite ≥ 75% compliance to oral bisphosphonate treatment in the past year and had a decrease in BMD as low as − 10.7% prior to enrollment. However, with a responder rate of 78% for IV IBN in the current study, it can be concluded that the remaining 22% were identified as true low responders.

Furthermore, a direct comparison cannot be made between this population of low responders and osteoporotic populations from other studies in Japan [12, 13, 25]. Nevertheless, the increase in lumbar spine BMD in the IV IBN (6 months, 1.92%; 12 months, 2.70%) and OBP (6 months, 1.98%; 12 months, 2.25%) in our study was numerically higher than that in the BP-MUSASHI study (50 mg/month oral minodronate, 1.5% at 6 months) [25] but numerically lower than that in the MOVER (0.5 and 1 mg/month IV ibandronate and 2.5 mg/day oral risedronate, 4–6% at 6 and 12 months) [13], MOVEST (100 mg/month oral and 1 mg/month IV ibandronate, 5.22% and 5.34%, respectively, at 12 months) [12], and post-marketing studies in Japanese patients with osteoporosis (1 mg/month IV ibandronate, 3.20% and 4.84% at 6 and 12 months, respectively) [15]. This could be attributed to the fact that the current study included low responders to oral bisphosphonates. However, caution should be advised for this interpretation as the study settings are not exactly the same: in the BP-MUSASHI study, patients switched from their previous bisphosphonates to 50 mg/month oral minodronate based on their preference [25]. The MOVER [13] and MOVEST [12] studies were not designed to assess the effectiveness of bisphosphonates in low responders.

Moreover, we observed a 2% increase in BMD in the OBP, which could be attributed to the following points. Of note, the compliance rate in the OBP was high (≥ 75% for 98% and 100% for 92% of the patients) throughout

IV IBN group	Category	n	% change lumbar spine BMD from baseline to 12 months	
			%	95%CI
Predefined subgroups				
eGFR	≥60	150	2.699	(2.077 - 3.321)
	<60	53	2.857	(1.864 - 3.851)
25-OH-VD3	≥15.9	90	2.695	(1.860 - 3.529)
	<15.9	113	2.651	(1.980 - 3.322)
Lumbar spine BMD at baseline	High	60	2.245	(1.321 - 3.168)
	Middle	77	2.753	(1.904 - 3.602)
	Low	70	3.030	(2.092 - 3.967)
Concomitant Vitamin D agents	Yes	124	2.552	(1.884 - 3.220)
	No	83	2.897	(2.078 - 3.715)
Post hoc subgroups				
Pre-used OBPs	Alendronate	35	2.034	(0.724 - 3.343)
	Minodronate	114	2.184	(1.552 - 2.816)
	Risedronate	57	4.241	(3.163 - 5.319)
Spondylosis deformans	Yes	25	3.918	(2.272 - 5.564)
	No	182	2.547	(2.005 - 3.090)

OBP group	category	n	% change lumbar spine BMD from baseline to 12 months	
			%	95%CI
Predefined subgroups				
eGFR	≥60	86	2.336	(1.534 - 3.139)
	<60	41	2.102	(1.150 - 3.054)
25-OH-VD3	≥15.9	61	2.212	(1.257 - 3.167)
	<15.9	66	2.373	(1.524 - 3.221)
Lumbar spine BMD at baseline	High	52	2.284	(1.256 - 3.313)
	Middle	37	2.866	(1.876 - 3.857)
	Low	41	1.644	(0.443 - 2.845)
Concomitant Vitamin D agents	Yes	74	2.763	(2.013 - 3.512)
	No	56	1.523	(0.492 - 2.555)
Post hoc subgroups				
Pre-used OBPs	Alendronate	29	2.441	(1.685 - 3.197)
	Minodronate	83	2.072	(1.184 - 2.959)
	Risedronate	18	2.744	(1.369 - 4.119)
Spondylosis deformans	Yes	20	3.174	(1.881 - 4.468)
	No	110	2.050	(1.355 - 2.744)

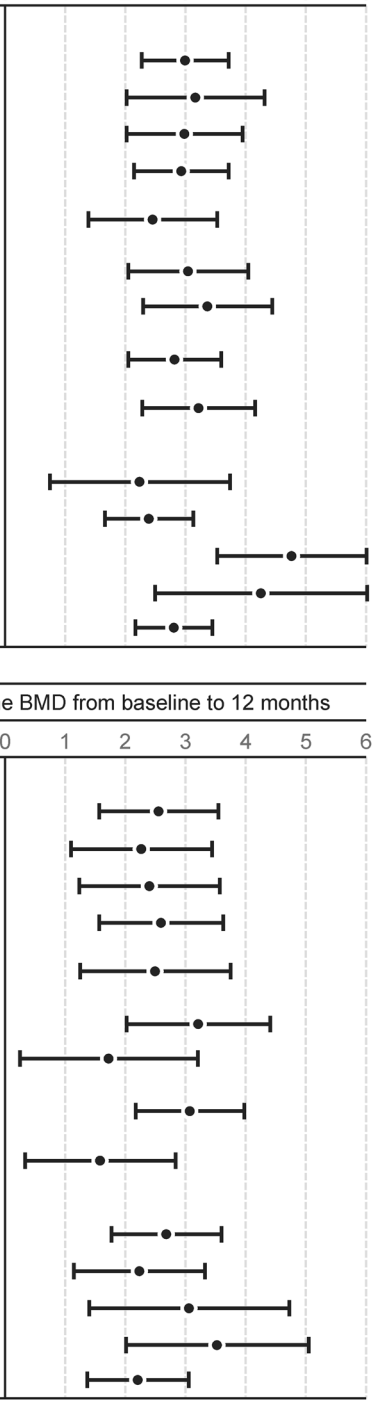

Fig. 3 Mean percent change from baseline to 12 months in lumbar spine BMD according to patient characteristics and comorbidity in IV IBN and OBP. *25-OH-VD$_3$* 25-hydroxyvitamin D_3, *BMD* bone mineral density, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *IV IBN* intravenous ibandronate group, *OBP* oral bisphosphonate group

the study period. The compliance rate before study participation (≥ 75%) was also higher than that reported in daily clinical practice in the United States (20–31% over 2 years) [26] and in Japan (38.6–77.7% over 1 year) [27]. Overall, the use of multiple oral bisphosphonates in the OBP with a compliance rate that increased from > 75%

Table 2 Baseline patient demographics and characteristics (matched cohort)

Characteristics	IV IBN ($n=108$)	OBP ($n=108$)	p value
Sex (female), *n* (%)	104 (96.3)	104 (96.3)	1.0000[b]
Age (years), mean ± SD	73.8 ± 7.8	74.0 ± 7.5	0.8317[d]
≥ 65 years, *n* (%)	96 (88.9)	97 (89.8)	0.8274[c]
Height (cm), mean ± SD	150.48 ± 6.06	150.88 ± 7.23	0.6541[d]
Body weight (kg), mean ± SD	49.84 ± 6.78	51.32 ± 8.42	0.1540[d]
BMI (kg/m^2), mean ± SD	22.007 ± 2.746	22.598 ± 3.730	0.1864[d]
Menopause[a], *n* (%)	104 (96.3)	104 (96.3)	–
Prevalent fracture, *n* (%)	56 (51.9)	57 (52.8)	0.8916[b]
Prevalent fragility fracture, *n* (%)	39 (36.1)	31 (28.7)	0.2448[b]
Current smoking, *n* (%)	6 (5.6)	7 (6.5)	0.7748[b]
Alcohol intake (≥ 3 units/day), *n* (%)	8 (7.4)	10 (9.3)	0.6225[b]
Lumbar spine BMD (L1–L4, g/cm^2), mean ± SD	0.701 ± 0.092	0.738 ± 0.125	0.0135[d]
Total hip BMD (g/cm^2), mean ± SD	0.688 ± 0.089	0.696 ± 0.095	0.5408[d]
sCTX (ng/ml), mean ± SD	0.143 ± 0.087	0.140 ± 0.102	0.8131[d]
TRACP-5b (mU/dL), mean ± SD	252.7 ± 103.3	245.6 ± 99.9	0.6072[d]
P1NP (μg/L), mean ± SD	20.57 ± 9.81	19.65 ± 9.29	0.4817[d]
sCa (mg/dL), mean ± SD	9.35 ± 0.46	9.40 ± 0.39	0.3615[d]
sCa (corrected, mg/dL), mean ± SD	9.39 ± 0.44	9.44 ± 0.37	0.4052[d]
Albumin (g/dL), mean ± SD	4.24 ± 0.29	4.26 ± 0.29	0.6533[d]
sP (mg/dL), mean ± SD	3.37 ± 0.54	3.36 ± 0.52	0.9007[d]
sCr (mg/dL), mean ± SD	0.648 ± 0.134	0.701 ± 0.181	0.0148[d]
eGFR (mL/min/1.73 m^2), mean ± SD	71.06 ± 14.98	66.22 ± 16.10	0.0230[d]
25-OH-VD$_3$ (ng/mL), mean ± SD	15.47 ± 5.02	15.82 ± 6.35	0.6499[d]
iPTH (pg/mL), mean ± SD	39.4 ± 16.3	40.9 ± 27.0	0.5999[d]

Data are presented as *n* (%) unless otherwise specified

25-OH-VD$_3$ 25-hydroxyvitamin D$_3$, *BMD* bone mineral density, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *iPTH* intact-parathyroid hormone, *IV IBN* intravenous ibandronate group, *NA* not available, *OBP* oral bisphosphonate group, *P1NP* procollagen type 1 amino-terminal pro-peptide, *sCa* serum calcium, *sCr* serum creatinine, *sCTX* serum C-telopeptide cross-link of type 1 collagen, *SD* standard deviation, *sP* serum phosphorus, *TRACP-5b* tartrate-resistant acid phosphatase isoform 5b

[a]One patient each in the IV IBN group and OBP group had unknown status for menopause

[b]Chi-square test

[c]Wilcoxon rank-sum test

[d]Two-sample *t* test

to nearly 100% post-enrollment may have contributed to the observed 2% increase in BMD. The drug compliance rate increased from > 75% to nearly 100% post-enrollment, indicating that drug compliance improved after study participation. It is possible that the compliance rate from the reports of questionnaire for patient has not exactly reported before registration of this study, and this report was less than actual rate. The collecting exactly drug adherence was difficult in questionnaire in routine clinical practice. It might be low compliance rate as less than 75%. Furthermore, the compliance rate might be increase after study registration because of the patient has received drug administration guidance by physician. Patients' high awareness of participation for clinical research and high self-motivation for treatment adherence were considered to result in even higher compliance compared with that prior to registration.

Furthermore, for both treatment groups, the background factors of the patients did not affect the increase in lumbar spine BMD at 12 months. Lumbar spine BMD increased significantly in the evaluated subgroups based on background factors. However, a remarkable increase in lumbar spine BMD was noted in patients who were switched from risedronate to the IV IBN. The bone metabolism of patient treated with risedronate returned to pre-treatment level early after stopping treatment compared with alendronate [28]. Not as much as risedronate, but ibandronate had also shown similar tendency [28]. The ibandronate and risedronate were classified in the same group as low affinity for hydroxyapatite [29]. On the other hand, the

Table 3 Matched cohort analysis (matched cohort)

Parameter	IV IBN Change from baseline (%), mean ± SD	OBP Change from baseline (%), mean ± SD	Estimated difference (95% CI)	*p* value
Lumbar spine BMD (L1–L4)				
6 months ($n=100$)	2.10 ± 2.99	1.77 ± 2.65	0.32 (−0.41, 1.05)	0.3838
12 months ($n=108$)	2.76 ± 3.38	2.27 ± 3.29	0.49 (−0.37, 1.36)	0.2611
Total hip BMD				
6 months ($n=81$)	0.50 ± 2.08	0.54 ± 2.29	−0.04 (−0.65, 0.57)	0.8935
12 months ($n=81$)	0.78 ± 2.04	0.85 ± 2.59	−0.08 (−0.83, 0.68)	0.8433
Femoral neck BMD				
6 months ($n=81$)	0.92 ± 3.32	0.61 ± 3.54	0.31 (−0.53, 1.15)	0.4710
12 months ($n=81$)	0.60 ± 3.69	0.78 ± 3.46	−0.18 (−1.33, 0.98)	0.7615
Trochanter BMD				
6 months ($n=81$)	0.52 ± 3.57	1.32 ± 4.25	−0.80 (−1.89, 0.29)	0.1482
12 months ($n=81$)	1.46 ± 3.44	1.62 ± 4.15	−0.16 (−1.35, 1.04)	0.7941
sCTX				
3 months ($n=104$)	4.77 ± 47.37	0.89 ± 39.12	3.88 (−7.07, 14.83)	0.4838
12 months ($n=103$)	17.59 ± 51.02	7.27 ± 55.52	10.33 (−3.82, 24.47)	0.1508
TRACP-5b				
3 months ($n=104$)	−2.36 ± 20.73	0.02 ± 15.83	−2.38 (−7.07, 2.30)	0.3149
12 months ($n=103$)	8.95 ± 25.58	9.34 ± 21.03	−0.39 (−6.93, 6.14)	0.9057
P1NP				
3 months ($n=104$)	−1.50 ± 27.39	1.24 ± 23.89	−2.74 (−9.75, 4.27)	0.4402
12 months ($n=103$)	10.01 ± 36.94	13.79 ± 28.75	−3.78 (−12.48, 4.92)	0.3905

BMD bone mineral density, *CI* confidence interval, *IV IBN* intravenous ibandronate group, *OBP* oral bisphosphonate group, *P1NP* procollagen type 1 amino-terminal pro-peptide, *sCTX* serum C-telopeptide cross-link of type 1 collagen, *SD* standard deviation, *TRACP-5b* tartrate-resistant acid phosphatase isoform 5b

Table 4 Safety overview (safety analysis)

Event	IV IBN ($n=235$)		OBP ($n=140$)	
	n (%)	Event, *n*	*n* (%)	Event, *n*
AEs	82 (34.9)	159	37 (26.4)	70
Injury, poisoning/procedural complications	31 (13.2)	51	5 (3.6)	7
Musculoskeletal/connective tissue disorders	27 (11.5)	30	10 (7.1)	12
Infections/infestations	23 (9.8)	27	14 (10.0)	19
Skin/subcutaneous tissue disorders	8 (3.4)	10	1 (0.7)	1
Gastrointestinal disorders	4 (1.7)	5	4 (2.9)	6
Renal/urinary disorders	1 (0.4)	1	2 (1.4)	3
Serious AEs	28 (11.9)	35	12 (8.6)	16
ADRs	9 (3.8)	9	3 (2.1)	3
Serious ADRs	2 (0.9)	2	0 (0.0)	0
AEs of special interest				
Hypercalcemia	0 (0.0)	0	2 (1.4)	2
Hypocalcemia	0 (0.0)	0	0 (0.0)	0
Osteonecrosis of jaw	0 (0.0)	0	0 (0.0)	0
Acute-phase reactions	2 (0.9)	3	0 (0.0)	0

ADR adverse drug reaction, *AE* adverse event, *IV IBN* intravenous ibandronate group, *OBP* oral bisphosphonate group

TRIO study demonstrated that the increase in lumbar spine BMD was greater with ibandronate and alendronate than with risedronate [30], and the MOTION study also showed that the effect on BMD was similar between ibandronate and alendronate [31]. Consequently, it is a possibility that the effect on lumbar spine BMD in patients with switched from risedronate to IV IBN was strongly increased, and the effect was similar ibandronate to alendronate.

There were no new safety concerns in the current study. AEs of injury, poisoning and procedural complications included those associated with fracture (e.g., spinal compression fracture, rib fracture, humerus fracture, and hand fracture). Similarly, common AEs reported as musculoskeletal and connective tissue disorders (e.g., osteoarthritis, arthralgia, and spinal osteoarthritis) were within the expected range in view of the nature of the osteoporotic patient population. Osteonecrosis of the jaw was not reported in any patient, and two patients in the OBP reported hypercalcemia. All reported APRs were mild in severity. The incidence of APRs in IV IBN [0.9% (2/235 patients)] was lower than that reported in the MOVEST study [11.8% (24/203 patients) in the 1 mg/month IV ibandronate (12)], which is attributable to the fact that patients in the current study had been treated with prior oral bisphosphonates before enrollment.

A between-group comparison of lumbar spine BMD revealed that the mean change from baseline to 12 months was numerically higher in IV IBN (2.70%) compared with OBP (2.25%), although no statistical comparison was made. This numerically higher increase (approximately 0.5%) in lumbar spine BMD in IV IBN may be attributed to the fact that patients in this group switched from their previous bisphosphonates (minodronate, alendronate, or risedronate) to a different molecule (ibandronate). Moreover, switching of the administration route (oral to IV) may have also contributed to the numerically higher increase in lumbar spine BMD. However, further investigation is warranted.

The present study has several limitations. First, the drug compliance rate for oral bisphosphonates before study registration was assessed in a subjective manner using patient interview. Second, the baseline characteristics and comorbidity of patients were not periodically re-evaluated during the study period. Lastly, patients categorized by duration of oral bisphosphonate treatment prior to enrollment were not evaluated. In conclusion, the present study demonstrated that switching to IV ibandronate from oral bisphosphonate significantly increased lumbar spine BMD, with no new safety concerns and no apparent increase in the nature or severity of ADRs. These findings suggest that switching to IV ibandronate due to no or low response to oral bisphosphonates may be clinically beneficial in daily practice for Japanese patients with primary osteoporosis.

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Author contributions HH designed the study and wrote the initial draft of the manuscript. Other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors contributed to analysis and interpretation of data, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

Conflict of interest H Hagino reports personal fees from Chugai Pharmaceutical Co., Ltd., during the conduct of the study; grants and other from Asahi Kasei Pharma Corp., Astellas Pharma Inc., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Corp., MSD K.K., Ono Pharmaceutical Co., Ltd., Pfizer Inc., Taisho Toyama Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Co., Ltd. and Daiichi Sankyo Co., Ltd.; and other from Eli Lilly Japan K.K., outside the submitted work. A. Sakai received research grants from Astellas Pharma Inc., Asahi Kasei Pharma Corp., Eisai Co., Ltd., Daiichi Sankyo Co., Ltd., Teijin Pharma Ltd., Chugai Pharmaceutical Co., Ltd., and MSD K.K., and lecture fees from Asahi Kasei Corp., Chugai Pharmaceutical Co., Ltd., and Taisho Toyama Pharmaceutical Co., Ltd., outside the submitted work. Y. Imanishi reports grants from Chugai Pharmaceutical Co., Ltd., during the conduct of the study; personal fees from Chugai Pharmaceutical Co., Ltd., outside the submitted work. H. Tsurukami reports personal fees from Chugai Pharmaceutical Co., Ltd., during the conduct of the study, and personal fees from Eli Lilly Japan K.K., outside the submitted work. S. Ikeda, S. Nakajo, and N. Miyakoshi have nothing to disclose.

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