



Original article

Safety and effectiveness of monthly intravenous ibandronate injections in a prospective, postmarketing, and observational study in Japanese patients with osteoporosis

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ABSTRACT

Objectives: This postmarketing, observational study evaluated the safety and effectiveness of monthly intravenous (IV) ibandronate in Japanese patients with osteoporosis.

Methods: Eligible patients received monthly IV ibandronate 1 mg for 12 months. Adverse drug reactions (ADRs) were evaluated. Changes in bone mineral density (BMD) and bone turnover markers (BTMs) were assessed using matched *t*-test analysis. Cumulative fracture rates were analyzed by Kaplan-Meier methodology.

Results: In total, 1062 patients were enrolled, of whom 1025 (n = 887 women, n = 138 men) were treated. Mean patient age was 77 years. Seventy-five ADRs were reported in 54 patients (5.26%). Four patients (0.39%) experienced serious ADRs, including one case of osteonecrosis of the jaw. Acute-phase reactions occurred in 21 patients (2.04%), and half of them arose after the first ibandronate injection. No new safety concerns were identified. Significant increases in BMD at 12 months relative to baseline were observed at the lumbar spine (4.84%, n = 187; 95% confidence interval [CI], 3.47%–6.21%), femoral neck (2.73%, n = 166; 95% CI, 1.46%–4.01%), and total hip (1.93%, n = 133; 95% CI, 0.80%–3.07%). Significant reductions were observed in all BTMs at 12 months (n = 174 in tartrate-resistant acid phosphatase-5b, n = 101 in procollagen type 1 N-terminal propeptide at baseline). The cumulative incidence of non-traumatic, new vertebral and nonvertebral fractures was 3.16% (95% CI, 2.12%–4.70%). Analyses in women only showed similar results to the overall population.

Conclusions: These findings confirm the favorable safety and consistent effectiveness of ibandronate, and indicate that monthly IV ibandronate would be beneficial in daily practice for the treatment of Japanese patients with osteoporosis.

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1. Introduction

Two formulations of ibandronate, monthly oral 150-mg tablet and quarterly intravenous (IV) 3-mg injection, have been commercially available in Western countries for more than a decade. These regimens have an annual cumulative exposure (ACE) ≥ 10.8 mg, which led to significant vertebral and nonvertebral

fracture risk reduction, as well as substantial bone mineral density (BMD) gains in earlier clinical studies [1,2]. The efficacy of these ibandronate regimens in significantly reducing the risk of vertebral, nonvertebral, and clinical fractures was also confirmed in meta-analyses of the clinical studies [3–7]. Quarterly IV ibandronate 3 mg injections were first approved in 2006 in the USA; to date, this formulation has been prescribed all over the world, excluding Japan.

In Japan, as in Western countries, bisphosphonates (BPs) are established as the first-line treatment of choice for osteoporosis. Once-monthly intermittent BP dosing regimens have been widely preferred by patients to more frequent administration [8]. Therefore, 2 monthly formulations of ibandronate, monthly IV 1 mg and

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monthly oral 100 mg, were developed to meet the medical preferences of Japanese patients. The MONTHly intraVenous ibandronate versus daily oral Risedronate (MOVER) registration study demonstrated the noninferiority of monthly IV ibandronate 1 mg (ACE of 12 mg) to oral risedronate in vertebral fracture risk reduction [9,10]. Monthly IV ibandronate consistently trended to reduce the incidence of not only vertebral fractures, but also nonvertebral fractures, compared with risedronate [9,11]. Monthly IV ibandronate 1 mg was approved in Japan as a bolus BP injection for the treatment of osteoporosis. The ACE of 12 mg is the same as that of quarterly IV ibandronate 3-mg injection, approved in Western countries. Monthly IV ibandronate has been prescribed to approximately 0.5 million Japanese patients with osteoporosis since it was made commercially available in 2013, and has led to improved treatment adherence, which may ultimately enhance clinical benefit [12,13]. Although the administration interval is different, both quarterly IV ibandronate 3 mg and monthly IV ibandronate 1 mg belong to the high ACE group (12 mg) [4,9] and have demonstrated comparable efficacy in fracture risk reduction and BMD gains.

Various pharmacovigilance actions must be taken when considering the safety and risk management of ibandronate in a real-world setting. For example, patient reminder cards are distributed to all patients via physicians to minimize the risk of osteonecrosis of the jaw (ONJ). In cases where this adverse drug reaction (ADR) occurs, patients are closely monitored using guided questionnaires. Accumulated safety data already exist for ibandronate and the risks associated with monthly IV ibandronate injection were listed in the Japanese risk-management plan. In addition, the manufacturer has been collating safety data from daily practice to feedback to physicians to optimize the use of ibandronate.

The aim of this multicenter, prospective, postmarketing, observational study was to examine the safety and effectiveness of monthly IV ibandronate for clinical use in a real-world setting. The study included not only women, but also men with osteoporosis, because a small group of male patients were assessed in the clinical development program.

2. Methods

2.1. Study design and population

This large-scale, multicenter, postmarketing, prospective, observational study (BON1301) examined the safety and effectiveness of monthly IV ibandronate 1 mg in Japanese women and men with osteoporosis in a real-world setting. A target of 1000 patients for recruitment to this study was set in order to provide data for accurate statistical estimation of the incidence of important ADRs, especially the incidence of acute-phase reactions (APRs), during the 1-year observation period. This was based on the registration clinical trial, the MOVER study. Patients were recruited from 257 hospitals and clinics including departments of orthopedic surgery and internal medicine. Eligible patients were diagnosed according to the diagnostic criteria of primary osteoporosis in Japan [14] and registered for the study (UMIN-CTR Clinical Trial number: UMIN000013412). Primary osteoporosis is defined by the World Health Organization as a BMD of T-score reduced by -2.5 standard deviations or more, whereas in Japan it is defined as a BMD of Young Adult Mean (YAM) reduced to less than or equal to 70%. In lumbar spine, femoral neck (FN), and total hip (TH), a BMD of 70% YAM is essentially the same as a BMD of T-score reduced by -2.5 standard deviations. Patients were not included in the study if they had any contraindications to ibandronate treatment, as described in the drug label, or if they had been treated with the drug before

participating in the study. All patients received monthly ibandronate 1 mg injections (Bonviva, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan), with an observation period of 12 months for women and 36 months for men. The study was conducted in accordance with good postmarketing study practice regulations from the Ministry of Health, Labour, and Welfare in Japan. The study protocol was approved by the relevant ethics committees and informed consent was obtained from individual participants included in the study. Here we describe the results of the 12-month observation period in women, which was from the start of the study in March 2014 to the cutoff date in January 2017. The 36-month observation period in men is still ongoing.

2.2. Safety assessments

ADRs and adverse events (AEs) of special interest, such as ONJ, APR, hypocalcemia, anaphylaxis, renal dysfunction, atypical femur fracture, and atrial fibrillation during treatment, were evaluated. The incidences of these ADRs were aggregated using preferred terms of the Medical Dictionary for Regulatory Activities. Estimated glomerular filtration rate (eGFR) values were measured every 3 months to determine any changes in renal function. All data were collated based on participating physician reports of spontaneous ADRs.

2.3. Effectiveness

The effectiveness of monthly IV ibandronate was assessed in terms of: BMD gains; suppression of bone turnover markers (BTMs); and the cumulative incidence of fractures. BMD measurements at the lumbar spine (L2–L4), TH, and FN were performed at baseline, 6, and 12 months using dual-energy x-ray absorptiometry. Missing data were imputed by the last observation carried forward method. Changes from baseline in BTMs of serum tartrate-resistant acid phosphatase-5b (TRACP-5b), serum N-telopeptide of type 1 collagen (NTX), serum procollagen type 1 N-terminal propeptide (P1NP), and serum bone-specific alkaline phosphatase (BAP) were measured. The date and location of nontraumatic vertebral and nonvertebral fractures, and clinical fractures were recorded and assessed according to radiographs. The incidence of vertebral fractures was assessed according to the radiographs taken at the 6- and 12-month visits.

2.4. Statistical analysis

Safety assessments were conducted in the safety population, which included all patients who received at least one injection of ibandronate. Assessments of effectiveness were conducted in the overall study population and in women only. Changes from baseline in BMD and BTMs, with 95% confidence intervals (CI), were recorded, and fracture incidence rates and corresponding 95% CIs were calculated. BMD and BTM values at 12 months were compared with those at baseline using matched *t*-test analysis, 2-sided with a significance level of 0.05. Adherence and cumulative fracture rates were assessed using Kaplan-Meier methodology. All statistical analyses were conducted using SAS System Release 9.2 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient disposition and baseline characteristics

In total, 1062 patients were enrolled, of whom 1025 patients ($n = 887$ women, $n = 138$ men) were treated and assessed. The clinical report records were not collected from 22 patients and the

Table 1
Baseline patient characteristics (n = 1025).

Characteristic	Value
Women	887 (86.5)
Age, yr	77.1 ± 9.0
<75	353 (34.4)
≥75	672 (65.5)
Weight, kg	49.1 ± 8.7
Women only	48.1 ± 8.3
Height, cm	150.2 ± 8.0
Women only	148.7 ± 7.0
Prevalent nonvertebral fractures	
Yes	57 (5.5)
No	968 (94.4)
Vertebral fractures	
1	141 (13.7)
>1	147 (14.3)
Previous osteoporosis drug treatment ^a	
Yes	515 (50.2)
No	510 (49.7)
Concomitant use of osteoporosis drugs	
Yes	569 (55.5)
Active vitamin D agents	510 (49.7)
Calcium agents	60 (5.8)
No	456 (44.4)
TRACP-5b, mU/dL	459.5 ± 215.3
Serum NTX, nmol BCE/L	22.9 ± 18.3
P1NP, µg/L	56.3 ± 34.8
BAP, µg/L	17.1 ± 10.0
Serum calcium adjusted, mg/dL	9.1 ± 0.5
eGFR, mL/min/1.73m ²	67.64 ± 20.62

Values are presented as number (%) or mean ± standard deviation.

TRACP-5b, tartrate-resistant acid phosphatase-5b; NTX, serum N-telopeptide of type 1 collagen; BCE, bone collagen equivalent; P1NP, procollagen type 1 N-terminal propeptide; BAP, bone-specific alkaline phosphatase; eGFR, estimated glomerular filtration rate.

^a Within 6 months of the start of the study.

safety assessment was not available in 15 other patients. Baseline patient characteristics are summarized in Table 1. The mean patient age was 77.1 years. Overall, 5.3% of patients had secondary osteoporosis that was caused by rheumatoid arthritis, diabetes, or other diseases. Overall, 50.2% of patients had received other osteoporosis agents prior to ibandronate and 55.5% of patients were receiving other osteoporosis agents (active vitamin D agents, 49.7%; calcium agents, 5.8%) concurrently with ibandronate.

3.2. Adherence with ibandronate treatment

The adherence rate with monthly IV ibandronate was 82.18% at the end of the 12-month treatment period (Fig. 1). Discontinuations occurred as a result of AEs (5.75%, n = 59) and other reasons (9.75%, n = 100).

3.3. Safety

In total, 75 ADRs occurred in 54 patients (5.26%) (4.97% women, 0.29% men; Table 2). The most common, all nonserious, ADRs (≥2 patients or 0.1%) were malaise (0.48%), injection-site pain, dizziness, headache, feeling abnormal, and abnormal hepatic function (all 0.29% each). There were no deaths on study, but four patients (0.39%) experienced serious ADRs, including one case each of ONJ, pneumonia, spinal compression fracture, and pubis fracture (all 0.09% each). The spinal compression fracture was classified as an ADR because causality to the drug was not denied by the participating physician. The case of ONJ occurred in a male patient who had poor oral hygiene, a long history of smoking and alcohol use, and had been receiving long-term treatment (3.5 years) with another BP prior to ibandronate. ONJ was diagnosed 4.5 months

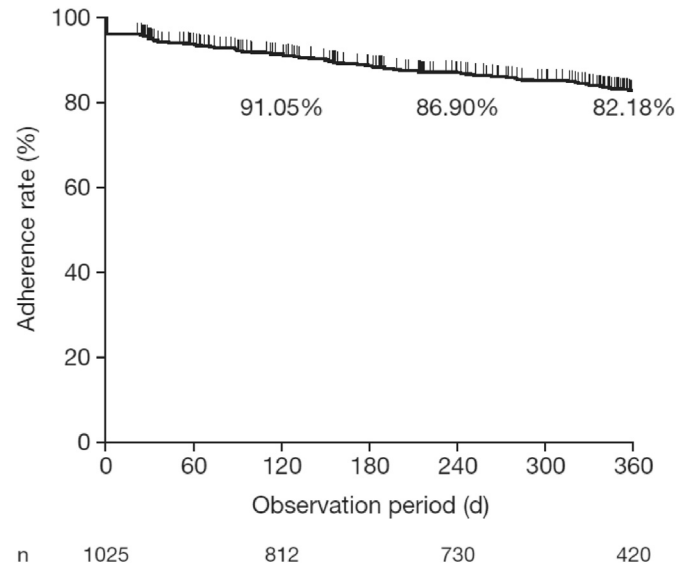


Fig. 1. Adherence rate with ibandronate treatment over 12 months.

Table 2
Summary of adverse drug reactions for ibandronate (n = 1025).

Variable	Number (%)
Drug-related ADRs	54 (5.26)
Women only	51 (4.97)
Men only	3 (0.29)
ADRs leading to death	0 (0)
Serious ADRs	4 (0.39)
Nonserious ADRs	50 (4.87)
AEs of special interest	
APR	21 (2.04)
ONJ	1 (0.09)
Hypocalcemia	0 (0)
Anaphylaxis	0 (0)
Renal impairment	0 (0)
Atypical femur fracture	0 (0)
Atrial fibrillation	0 (0)
Most common ADRs ^a	
Malaise	5 (0.48)
Dizziness	3 (0.29)
Headache	3 (0.29)
Abnormal hepatic function	3 (0.29)
Feeling abnormal	3 (0.29)
Injection-site pain	3 (0.29)
Pneumonia	2 (0.19)
Nausea	2 (0.19)
Oral discomfort	2 (0.19)
Stomatitis	2 (0.19)
Rash	2 (0.19)
Arthralgia	2 (0.19)
Back pain	2 (0.19)
Pyrexia	2 (0.19)
Injection-site swelling	2 (0.19)
Increased blood urea	2 (0.19)
Spinal compression fracture	2 (0.19)

ADR, adverse drug reaction; AE, adverse event; APR, acute-phase reaction; ONJ, osteonecrosis of the jaw.

^a Occurring in ≥0.1% of patients.

after starting ibandronate; treatment was withdrawn but the ONJ remained unresolved at the end of the follow-up period. APRs were reported in 21 patients (2.04%), half of which occurred after the first ibandronate injection. Most APRs were mild in intensity and transient, and decreased with each subsequent dose of medication. No change in eGFR levels was noted throughout the 12-month treatment period (Supplementary Fig. 1) and there were no reported

special interest AEs of renal function, hypocalcemia, anaphylaxis, atypical fracture of the femur, or atrial fibrillation (Table 2).

3.4. Bone mineral density

The time course change of BMD gains was evaluated by site (L2–L4, TH, and FN). The mean BMD changes were 3.20% (n = 183; 95% CI, 2.40%–4.01%) at 6 months and 4.84% (n = 187; 95% CI, 3.47%–6.21%) at 12 months from baseline (n = 248) at L2–L4, 1.31% (n = 129; 95% CI, 0.16%–2.47%) at 6 months and 1.93% (n = 133; 95% CI, 0.80%–3.07%) at 12 months from baseline (n = 168) at the TH, and 1.52% (n = 160; 95% CI, 0.58%–2.47%) at 6 months and 2.73% (n = 166; 95% CI, 1.46%–4.01%) at 12 months from baseline (n = 219) at the FN. The mean BMD changes from baseline to 6 and 12 months, respectively, in women only are shown in Fig. 2. All BMD gains were statistically significant compared with baseline values.

Overall, 515 patients (50.2%) had previously been treated with osteoporosis drugs including other BPs (Table 1). Of these, 166 patients (16.1%) were treated with other BPs. The mean BMD changes at the lumbar spine were 4.15% (95% CI, 1.43%–6.87%) in other BP-treated patients and 6.12% (95% CI, 3.13%–9.11%) in patients receiving other osteoporosis treatments at 12 months from baseline, compared with 4.04% (95% CI, 2.61%–5.47%) in treatment-naïve patients. Activated vitamin D drugs had been concomitantly prescribed to 510 patients (49.7%) (Table 1). The mean BMD changes at the lumbar spine were 4.88% (95% CI, 3.53%–6.23%) at 12 months from baseline in women only who were treated with active vitamin D agents, compared with 3.00% (95% CI, 1.63%–4.37%) in the treatment-naïve women.

3.5. Bone turnover markers

The time course change of TRACP-5b, NTX, P1NP, and BAP levels was evaluated in 540 patients. Mean changes in BTM were –30.46% (n = 114; 95% CI, –35.35% to –25.58%) at 6 months and –30.42% (n = 97; 95% CI, –37.40% to –23.45%) at 12 months from baseline (n = 174) for TRACP-5b, –12.56% (n = 43; 95% CI, –19.84% to –5.29%) at 6 months and –18.73% (n = 31; 95% CI, –30.71% to –6.75%) at 12 months from baseline (n = 52) for NTX, –33.87% (n = 62; 95% CI, –47.16% to –20.59%) at 6 months and –44.62% (n = 59; 95% CI, –55.30% to –33.95%) at 12 months from baseline (n = 101) for P1NP, and –27.81% (n = 68; 95% CI, –35.37% to –20.25%) at 6 months and –36.15% (n = 57; 95% CI, –43.61% to –28.68%) at 12 months from baseline (n = 81) for BAP. The mean BTM changes from baseline to 6 and 12 months, respectively, in women only are shown in Fig. 3. A significant decrease from baseline was observed at 6 and 12 months for all of the values measured.

3.6. Fracture incidence

The cumulative incidence of nontraumatic, vertebral and nonvertebral fractures in all 1025 patients was 1.41% (95% CI, 0.80%–2.48%) at 6 months and 3.16% (95% CI, 2.12%–4.70%) at 12 months. The corresponding incidences in women only were 1.39% (95% CI, 0.75%–2.58%) and 3.07% (95% CI, 1.98%–4.73%), respectively (Fig. 4A). The cumulative incidence of all nonvertebral fractures was 0.95% (95% CI, 0.47%–1.89%) at 6 months and 1.81% (95% CI, 1.07%–3.05%) at 12 months. The incidences in women only were 0.96% (95% CI, 0.46%–2.01%) and 1.80% (95% CI, 1.02%–3.16%), respectively (Fig. 4B). The incidences of the major three (femur, forearm, and humerus) nonvertebral fractures in the overall population and in women only were 1.00% (95% CI, 0.50%–1.99%) and 0.86% (95% CI, 0.38%–1.92%), respectively. Incidences of the major six

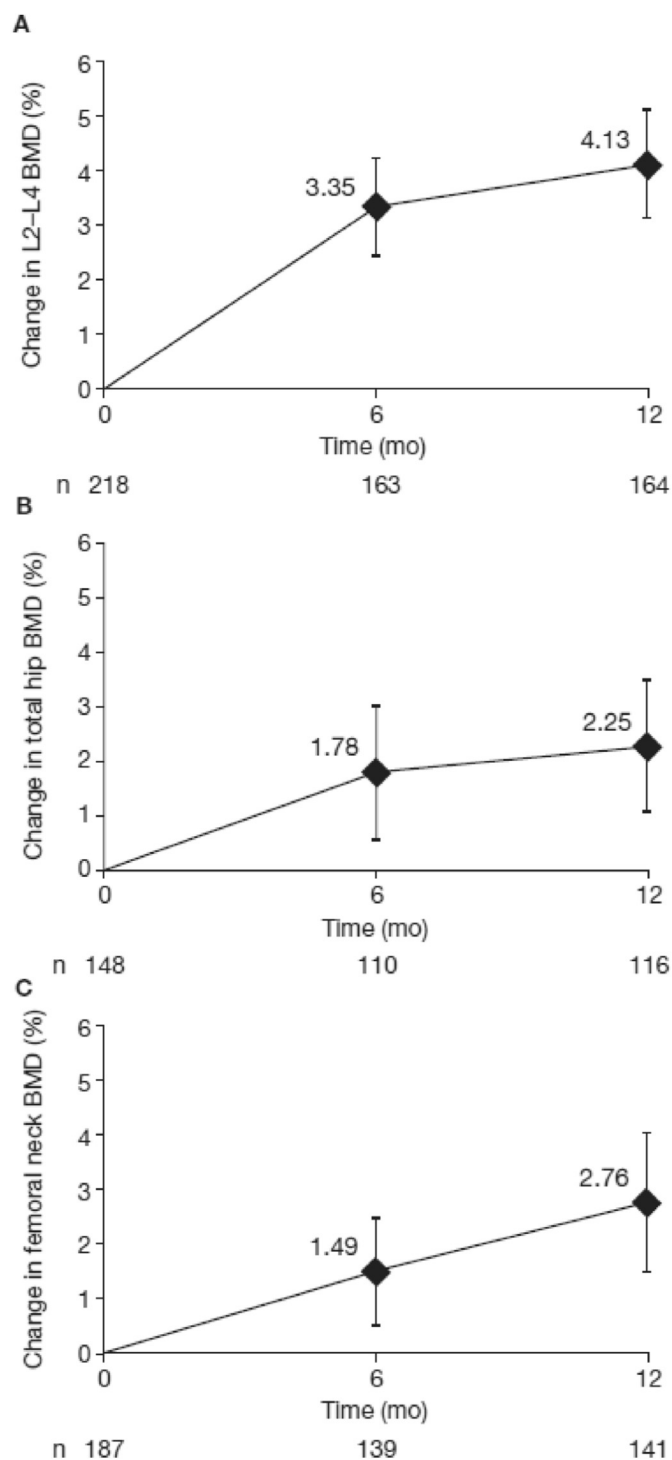


Fig. 2. Mean relative change in bone mineral density (BMD) from baseline to 12 months (with 95% confidence interval) in women only at: (A) lumbar spine (L2–L4) ($P < 0.0001$ vs. baseline at 6 and 12 months); (B) total hip ($P = 0.0069$ vs. baseline at 6 months, $P = 0.0003$ vs. baseline at 12 months); and (C) femoral neck ($P = 0.0037$ vs. baseline at 6 months, $P < 0.0001$ vs. baseline at 12 months).

nonvertebral fractures (forearm, femur, humerus, pelvis, leg, and clavicle) in the overall population and in women only showed similar values. The cumulative incidence of clinical fractures was 1.64% (95% CI, 0.97%–2.75%) at 6 months and 3.47% (95% CI, 2.39%–5.04%) at 12 months. In women only, these values were 1.65% (95% CI, 0.94%–2.89%) and 3.43% (95% CI, 2.28%–5.13%), respectively

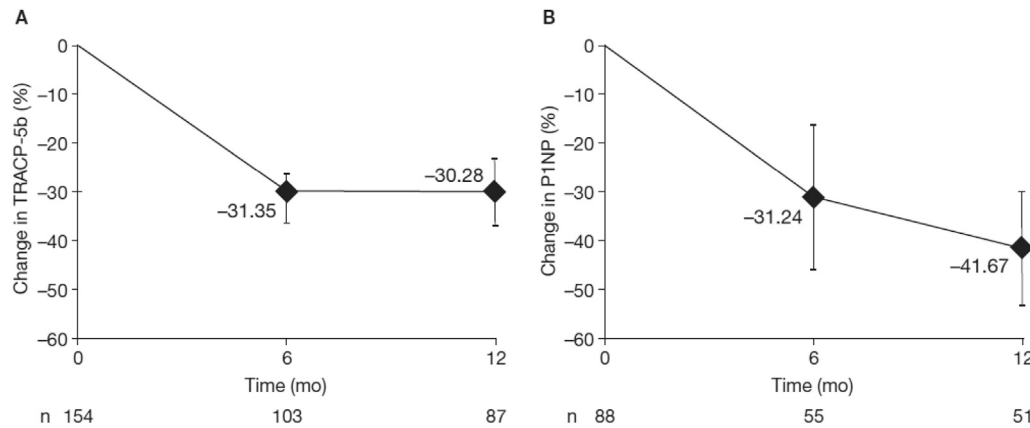


Fig. 3. Mean relative change from baseline to 12 months (with 95% confidence interval) in women only in: (A) TRACP-5b ($P < 0.0001$ vs. baseline at 6 and 12 months) and (B) P1NP ($P < 0.0001$ vs. baseline at 6 and 12 months). P1NP, procollagen type 1 N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase-5b.

(Fig. 4C). The incidence of vertebral fractures was 1.64% (95% CI, 0.78%–3.42%) at 6 months and 3.44% (95% CI, 2.00%–5.87%) at 12 months in the overall population, and 1.63% (95% CI, 0.73%–3.60%) and 3.34% (95% CI, 1.86%–5.99%), respectively, in women only.

4. Discussion

We performed a prospective, multicenter, postmarketing, observational study to examine the safety and effectiveness of monthly IV ibandronate 1 mg in a Japanese real-world setting. Our results showed a safety profile for ibandronate that is similar to previous studies performed with both Western and Japanese patients, with no apparent increase in the nature or severity of ADRs.

APR is commonly experienced following the first administration of intermittent nitrogen-containing BP and is one of the identified risks of ibandronate. In the Japanese MOVER study, the range of symptoms that included specific (e.g., myalgia) and nonspecific (e.g., back pain, headache) drug-related AE terms was evaluated by onset (within 3 days of dosing) and duration (≤ 7 days) [9]. In the real-world setting, symptoms defined as APR were mild to moderate in intensity, transient, and approximately half were associated with the first ibandronate administration, as reported previously [2]. Twenty patients with APR in the current study recovered well, but information on one patient was missing. The frequency of APRs in our study (2.0% over 12 months) was lower than reported in the MOVER study (7.1%, as drug-related AEs, over 3 years) [9]. A recent report compared the incidence of APRs between once-yearly zoledronic acid infusion and quarterly IV ibandronate in a real-world setting: the APR incidence of zoledronic acid was significantly higher than ibandronate in BP-naïve patients [15]. This might be due to specific compound or formulation issues. Of 21 patients with APR in the current study, 18 patients were BP-naïve and 3 patients were pretreated with another BP other than ibandronate. This suggests that physicians should be aware of the risk of APR when prescribing ibandronate and provide detailed safety information, particularly to treatment-naïve patients.

Renal dysfunction is a known ADR with BPs. However, no renal-related ADRs were observed in this study and the levels of eGFR did not change throughout the study period. Similarly, in the prospective, randomized, open-label, multicenter Designed for IV Ibandronate reNal safety Evaluation (DIVINE) study, treatment with quarterly IV ibandronate 3 mg for 12 months resulted in no eGFR changes in a primary care setting in postmenopausal, osteoporotic women at higher risk for renal disease [16]. Careful administration of monthly IV ibandronate is recommended in patients with severe renal disorders (< 30 eGFR mL/min/1.73 m²) as excretion may be

delayed. Additional exploratory research is being conducted in patients with severe renal disorders in Japan.

BMD gains at all sites were substantial and significantly improved over baseline values in the current study. Treatment with IV ibandronate resulted in similar BMD gains as obtained in the MOVER and Monthly Oral VErSUS intravenous ibandronate (MOVEST) studies [9,17]. BMD gains at the FN increased significantly with monthly IV ibandronate, as previously reported [10]. In comparison, FN BMD increased by 1.52% and 2.40% at 6 and 12 months, respectively, in the MOVER study, and by 1.78% and 2.25%, respectively, in the current study. The relationship between BMD gains and fracture risk reduction with ibandronate has been reported previously [18,19]. The fact that BMD gains were substantial at all sites in this study supports a notion that monthly IV ibandronate is efficacious in fracture risk reduction.

When the patients were previously treated with other BPs or other osteoporosis drugs before entering the study, the BMD gains appeared similar between the treatment-naïve and previously treated patients, although the patient numbers were small after subgrouping. Concerning the concomitant use of osteoporosis drugs, activated vitamin D drugs had been concomitantly prescribed to 510 patients (49.7%). Of these, 370 patients were treated with eldcalcitol, which has been prescribed most frequently in Japan as an activated vitamin D drug. It was reported that combined treatment with eldcalcitol and BP gave rise to higher BMD increases than treatment with native vitamin D and BP [20].

A rapid reduction in bone resorbing markers was generally seen within 3 months, and the levels at 6 and 12 months were comparable for both TRACP-5b and NTX. The levels of bone formation markers decreased more gradually than the bone resorbing markers, and the levels of P1NP and BAP showed the same time-course of reduction as each other.

The reported incidence of vertebral fractures in Japan is approximately 2%–9% per year in women aged ≥ 70 years, regardless of fracture prevalence [21]. Compared with the previous clinical study assessing the cumulative incidence of first new vertebral fractures in elderly Japanese women with osteoporosis [9], we observed a lower incidence of vertebral fractures in women only in our study (1.63%–3.34%). However, differences in study population and fracture assessment procedure (individual or central) are to be noted.

There are some limitations to this study. As it was a real-world study there was no comparator or control arm. The study was conducted in multiple institutions (hospitals and clinics) in daily practice, and efficacy evaluations were not performed by a central committee. The BMD and BTM data were not assessed for all of the

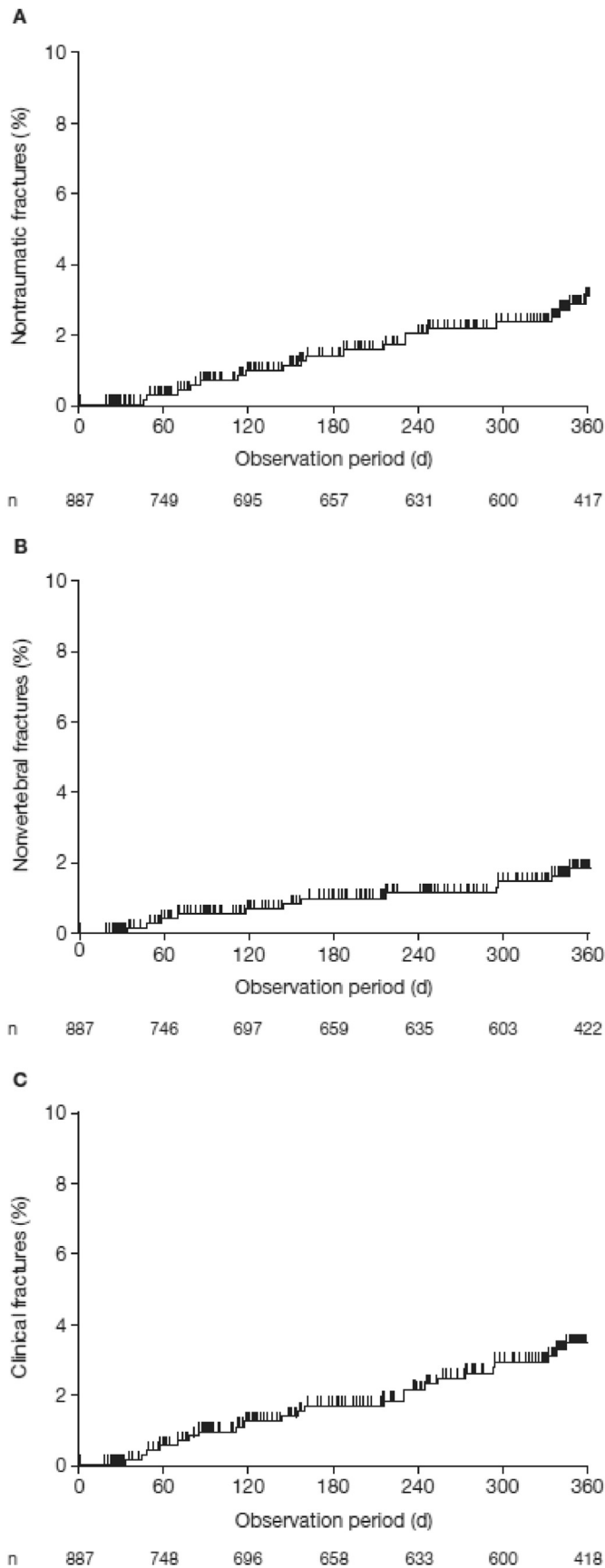


Fig. 4. Fracture incidence through 12 months of ibandronate treatment in women only: (A) nontraumatic vertebral and nonvertebral fractures; (B) all nonvertebral fractures; and (C) clinical fractures.

patients. In addition, some patients had secondary osteoporosis, although there were only 55 cases (5.3%). Due to the expansion and penetration of BP therapy in Japan, the proportion of patients with prior history of BP treatment is increasing. Therefore, data on subgroup analysis according to patient characteristics, such as pretreatment history, will be conducted and reported in the future. In the MOVER study, a small number of men were enrolled, but only results in the overall population and in women have been reported [9]. Another aim of this current study was to investigate the safety and effectiveness of ibandronate in men following 3 years of treatment; the observation period in men is still ongoing.

5. Conclusions

The results of this observational study provide clinical information regarding the unique ibandronate regimen in Japan, monthly IV injection, in daily practice. The safety and effectiveness of monthly IV ibandronate in Japanese patients is well established and is supported by a clinical development program, and now by this postmarketing observational data. The benefit-risk profile of monthly IV ibandronate is positive in currently approved indications in Japan. No additional pharmacovigilance or risk minimization actions are needed, and its use in daily practice should lead to clinical benefit for patients with osteoporosis.

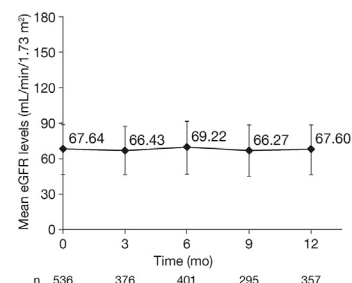
Conflicts of interest

This registry study was sponsored by Chugai Pharmaceutical Co., Ltd. Y. T. has disclosed that he received research grants from Chugai Pharmaceutical Co., Ltd. and Daiichi-Sankyo Inc., and is a member of the speakers' bureau for Chugai Pharmaceutical Co., Ltd., Daiichi-Sankyo Inc., Teijin Pharma Ltd., and Asahikasei Pharma Corp. J. H., Y. N., C. Y., T. T., and A. A. have disclosed that they are employees of Chugai Pharmaceutical Co., Ltd. No other potential conflict of interest relevant to this article was reported.

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Supplementary material



Supplementary Fig. 1. Time course change of mean (±standard deviation) eGFR levels from baseline to 12 months. eGFR, estimated glomerular filtration rate.

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