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Original article

Efficacy, safety, and compliance of ibandronate treatment for 3 years in postmenopausal Japanese women with primary osteoporosis

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ABSTRACT

Objectives: The aim of this study was to examine the efficacy, safety, and adherence of ibandronate (IBN) treatment with or without vitamin D supplementation for 3 years in Japanese women with postmenopausal osteoporosis.

Methods: This prospective investigation included 27 patients treated with IBN alone (monotherapy group) and 29 patients receiving IBN and alfacalcidol (ALF) (combination group). Bone metabolism and bone mineral density (BMD) were measured before and at 18, 24, 30, and 36 months of therapy. Treatment discontinuation and fracture occurrence were assessed as well.

Results: Lumbar 1–4 BMD (L-BMD) was significantly increased in the monotherapy and combination groups by 3.9% and 7.2%, respectively, at 36 months, with significant gains in total hip BMD (H-BMD) of 3.7% and 4.9%, respectively. There were significant differences in L-BMD improvement between the groups at 18, 24, and 30 months ($P < 0.05$) and at 36 months ($P < 0.01$). Compared with pretreatment levels, the percentage changes of L-BMD and H-BMD were significant at all time points in the combination group and at all points apart from L-BMD at 36 months in the monotherapy group. In the monotherapy group, 14 patients dropped out during 3 years and 2 vertebral fractures occurred during the first year. In the combination group, 16 cases dropped out during 3 years and 1 nonvertebral fracture was noted during the first year.

Conclusions: Our findings suggest that combination therapy of IBN and vitamin D is superior to monotherapy with regard to L-BMD improvements for 3 years, with both groups showing comparable safety and adherence to treatment.

1. Introduction

Osteoporosis is a worldwide health problem related to the aging population and is often underdiagnosed and undertreated. It is also an important global public health concern with both societal and economic implications [1].

Osteoporotic fractures, including vertebral, hip, and wrist fractures, are common. The lifetime risk of fracture incidence is higher in women than in men; the 10-year fracture risk at 50 years of age is 9.8% in women and 7.1% in men, which increases to 21.7% and 8%, respectively, by 80 years of age [2]. Hip fractures are particularly associated with significantly increased mortality rates, with most deaths occurring within 3–6 months after the event [3]. Thus, appropriate osteoporosis treatment and the prevention of osteoporotic fractures are important to ensure adequate levels of activities of daily life and quality of life.

Dozens of osteoporotic drugs have been developed to date. Many patients with osteoporosis are treated with the sequential use of 2 or more therapies [4,5]. Among the most current drug options, the intravenous bisphosphonate (BP) ibandronate (IBN) has recently and widely been used for the treatment of primary and secondary osteoporosis [6,7]. Previous reports have demonstrated the short-term usefulness and safety of IBN treatment in Japanese osteoporosis patients [6,7], although 3-year prospective study using IBN has been reported previously [8], the additive effects of active vitamin D on IBN treatment is largely unknown.

Our earlier study demonstrated that up to 18 months of continuous IBN treatment in postmenopausal women was well

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tolerated and associated with persistent gains in bone mineral density (BMD) and reductions in bone turnover markers. Moreover, combined therapy of IBN and active vitamin D in the form of alfacalcidol (ALF) increased BMD significantly more than did IBN alone for 18 months, suggesting combination therapy (BPs plus vitamin D) as more effective than monotherapy (BPs alone) for osteoporosis treatment [7]. There is increasing interest in the long-term effects of antiosteoporotic treatments and it has become essential to confirm key results. Thus, we extended our 18-month trial [7] to 3 years to comparatively investigate the efficacy, safety, and compliance of IBN mono- and combination therapy.

2. Methods

In this prospective, simple randomized study by an enveloped method, 56 postmenopausal Japanese women with primary osteoporosis were enrolled as out-patients at our institutions between 2014 and 2017.

The inclusion criteria for the study were postmenopausal Japanese women with primary osteoporosis and low lumbar 1–4 vertebrae BMD (L-BMD) and/or bilateral total hip BMD (H-BMD) of a T score of less than 2.5 standard deviation. Exclusion criteria were the presence of chronic renal failure (estimated glomerular filtration rate <40 mL/min/1.73 m^2), bone metabolic disorder, or diabetes mellitus, all of which could affect osteoporosis, along with fracture within 1 year prior to the study. The diagnosis of osteoporosis was made in accordance with the revised criteria established by the Japanese Society of Bone and Mineral Research [9]. Our cohort included 27 patients treated with IBN alone (monotherapy group) and 29 patients who received IBN and ALF (combination group). Of the 56 participants, 14 of 27 in the monotherapy group for unknown reasons (2 cases), economic reasons (2 cases), dental treatment (3 cases), admission to a nursing home (2 cases), hospitalization for another disease (2 cases), transfer to another hospital (3 cases), and 16 of 29 in the combination group for unknown reasons (2 cases), economic reasons (1 case), dental treatment (2 cases), admission to a nursing home (2 cases), hospitalization for another disease (2 cases), transfer to another hospital (4 cases), and death (3 case) dropped out according to exit interviews with physicians when applicable. Consequently, 13 cases in each group were left for further analysis.

Thirteen cases in each group participated at every time point throughout this study. Prior to this study, 1 patient took alendronate (ALN), 1 patient took risedronate (RIS), and 3 patients took minodronate (MIN) in the monotherapy group and 2 patients took ALN, 1 patient took RIS, and 1 patient took MIN in the combination group. We did not examine the effects of individual BP drugs since they were routinely changed for patients exhibiting low responsiveness.

All patients received 1.0 mg of IBN by monthly intravenous injection. In the combination group, patients were also prescribed 1.0 μg of oral ALF daily after their morning meal.

Serum levels of bone alkaline phosphatase (BAP) and N-terminal propeptide of type 1 procollagen (P1NP) were measured as bone-formation markers using a chemiluminescent enzyme immunoassay and antibody radioimmunoassay. Serum levels of tartrate-resistant acid phosphatase (TRACP)-5b and urinary levels of N-terminal telopeptide of type-I collagen (NTX) (Osteomark, Ostex International, Seattle, WA, USA) were evaluated as markers of bone resorption using an enzyme-linked immunosorbent assay. Each marker was assessed at baseline just before IBN administration and at 18, 24, 30, and 36 months of treatment. After overnight fasting, serum and first-void urine samples were collected between 8:30 a.m. and 10:00 a.m. Immunoassays were carried out by SRL (Tokyo, Japan).

The percentage changes of BMD were calculated using a dual-energy X-ray absorptiometry fan-beam bone densitometer (Lunar Prodigy; GE Healthcare, Waukesha, WI, USA) at the L1–4 levels of the posteroanterior spine and at the bilateral total hips at baseline just before IBN administration and at 18, 24, 30, and 36 months of treatment.

Bone turnover markers and BMD results are expressed as the mean ± standard error of the mean. For both groups, we compared the changes in markers, L-BMD, and H-BMD at each time point using the Bonferroni correction method for multiple comparisons. Comparisons of these parameters between the test groups at each measurement point were performed using Welch's *t*-test. Differences were considered statistically significant at $P < 0.05$.

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee. This investigation was carried out in accordance with the ethical standards set forth in the Declaration of Helsinki (2014 revision). Written consent was obtained from all patients prior to the start of the study. The ethics committee of Showa-Inan General Hospital reviewed and approved the study protocol. This investigation was approved by Clinical Trials.gov (NCT02156999; registration date: June 1, 2014).

3. Results

There were no significant differences in baseline patient age, body mass index, bone turnover marker values, serum active vitamin D values, or BMD values between the groups (Table 1). No serious adverse effects, such as atypical fracture or hypocalcaemia, occurred during the 3-year observational period.

3.1. Changes of bone turnover markers and BMD

3.1.1. Markers of bone formation

The percentage changes of BAP and P1NP were significantly inhibited throughout the study period in both groups ($P < 0.01$) compared with pretreatment levels. There were no significant differences between the groups during the observational period (Fig. 1A, B).

3.1.2. Markers of bone resorption

The percentage changes of TRACP-5b and urinary NTX were significantly inhibited at 18, 24, and 30 months in both groups ($P < 0.01$) compared with pretreatment levels. The percentage changes of TRACP-5b in the combination group at 36 months

Table 1
Patient characteristics prior to the start of ibandronate therapy.

Characteristic	IBN (n = 27)	IBN with ALF (n = 29)
Age, yr	71.4 ± 1.9	71.2 ±2.1
Sex, female:male	27: 0	29: 0
Body mass index, kg/m^2	21.3 ± 0.6	21.1 ±0.7
Serum corrected Calcium, mg/dL	9.2 ± 0.1	9.2 ± 0.1
Serum Phosphorus, mg/dL	3.6 ± 0.1	3.6 ± 0.1
Serum BAP, μg/L	20.9 ± 2.67	22.0 ±2
Serum P1NP, mU/dL	67.4 ± 7.7	72.2 ±8.5
Serum TRACP-5b, mU/dL	603.3 ± 46.7	600.7 ± 47.0
Urinary NTX, nmol BCE/mmol/CRE	47.9 ± 5.6	44.2 ±3.3
1, 25 $(OH)_2D_3$, pg/mL	58.9 ± 3.1	57.1 ±2.9
Serum whole PTH	32.9 ± 2.7	33.3 ±2.8
Lumbar 1–4 BMD, g/cm^2	0.811± 0.03	0.810 ± 0.03
Total hip BMD, g/cm^2	0.669 ± 0.02	0.672 ± 0.02

Values are presented as mean ± standard error.
BAP, bone-specific alkaline phosphatase; P1NP, N-terminal propeptide of type I procollagen; TRACP-5b, tartrate-resistant acid phosphatase 5b; NTX, type I collagen cross-linked N-telopeptide; BMD, bone mineral density.

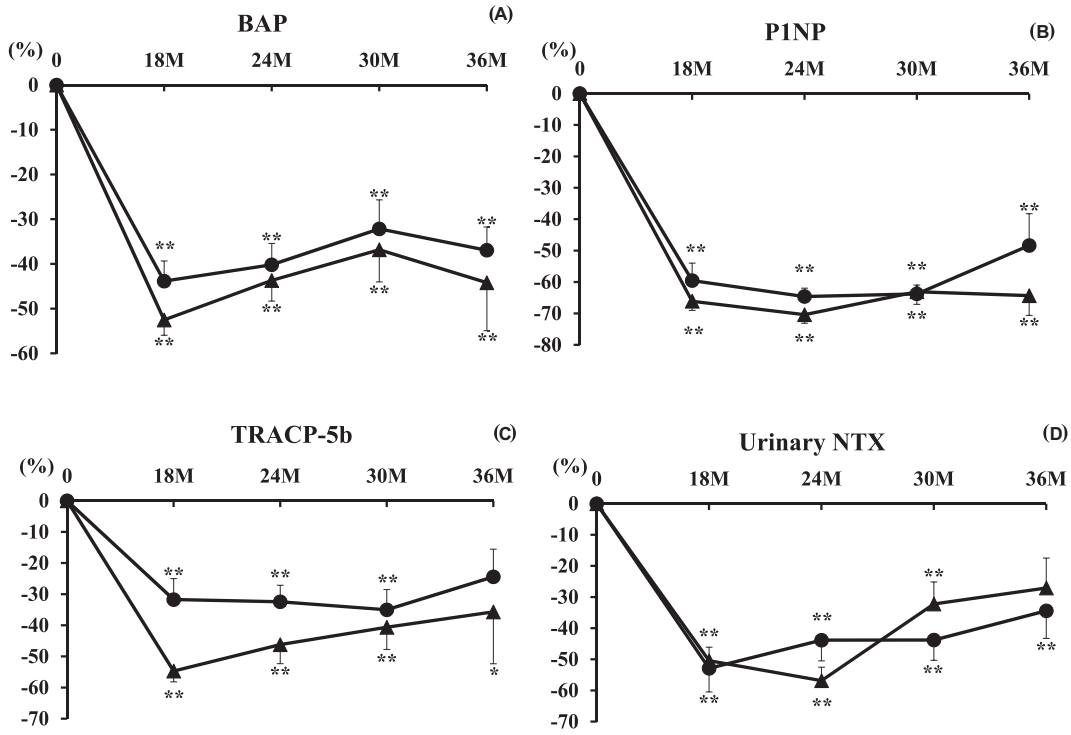

Fig. 1. Percentage changes of bone specific alkaline phosphatase (BAP), N-terminal propeptide of type 1 procollagen (P1NP), tartrate-resistant acid phosphatase (TRACP)-5b, and urinary N-terminal telopeptide of type-I collagen (NTX) for 3 years. The percentage changes of BAP (A) and P1NP (B) were significantly and comparably inhibited throughout the study period in both groups ($P < 0.01$) compared with pre-treatment levels. The percentage changes of TRACP-5b (C) and urinary NTX (D) were significantly inhibited at 18, 24, and 30 months in both groups ($P < 0.01$) compared with pretreatment levels. The percentage changes of TRACP-5b in the combination group at 36 months ($P < 0.05$) (C) and urinary NTX in the monotherapy group at 36 months ($P < 0.01$) (D) were also significantly inhibited versus baseline. There were no significant differences between the groups during the observational period. *$P < 0.05$ and **$P < 0.01$, significant differences compared with pretreatment values.

($P < 0.05$) and those of urinary NTX in the monotherapy group at 36 months ($P < 0.01$) were also significantly inhibited. There were no significant differences between the groups during the observational period (Fig. 1C and D).

3.1.3. L-BMD and H-BMD findings

The percentage changes of L-BMD were significantly increased in the combination group during the entire study period ($P < 0.01$) compared with pretreatment values. In the monotherapy group, these changes were significantly increased at 18, 24, and 30 months ($P < 0.05$) . There were significant differences between the groups at 18, 24, 30 months ($P < 0.05$) and at 36 months ($P < 0.01$) of therapy (Fig. 2A). The percentage changes of L-BMD in the monotherapy and combination groups were 3.9% and 7.2%, respectively, at 36 months (Fig. 2A).

The percentage changes of H-BMD were significantly increased in both groups during the entire study period ($P < 0.01$) compared with pretreatment levels. There were no significant differences between the groups throughout the study period (Fig. 2B). The percentage changes of H-BMD in the monotherapy and combination groups were 3.7% and 4.9%, respectively, at 36 months (Fig. 2B).

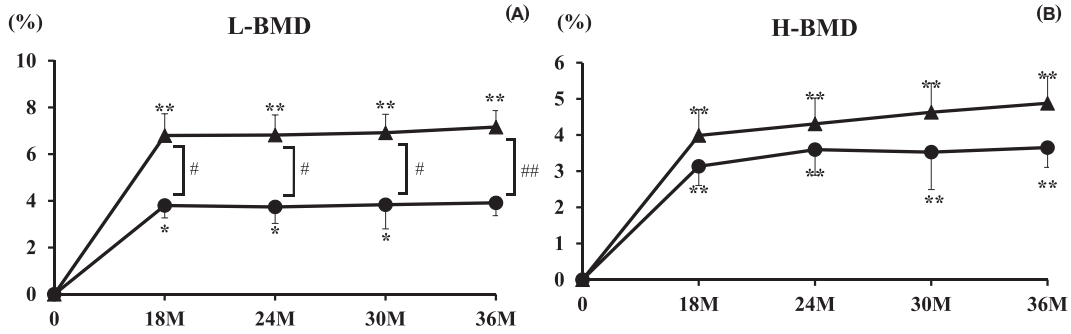

Fig. 2. Percentage changes of bone mineral density (BMD) at the lumbar 1–4 spine (L-BMD) and bilateral total hips (H-BMD) for 3 years. Closed circles show the monotherapy group and closed triangles show the combination group. (A) The percentage changes of L-BMD were significantly increased in the combination group during the entire study period ($P < 0.01$) compared with pretreatment values, while those in the monotherapy group were significantly increased at 18, 24, and 30 months ($P < 0.05$). There were significant differences between the groups at 18, 24, and 30 months ($P < 0.05$) and at 36 months ($P < 0.01$). (B) The percentage changes of H-BMD were significantly increased in both groups throughout the study period ($P < 0.01$) compared with pretreatment levels. There were no significant differences between the groups throughout the study period. *$P < 0.05$ and **$P < 0.01$, significant differences compared with pretreatment values. #$P < 0.05$ and ##$P < 0.01$, significant differences between the groups at indicated time points.

3.2. Compliance and fracture occurrence during IBN treatment

The number of patients who completed this 3-year investigation was 13 of 27 (48.1%) in the monotherapy group and 13 of 29 (44.8%) in the combination group. There were no remarkable differences in the characteristics of dropout patients.

In the monotherapy group, 14 cases dropped out (51.9%) for unknown reasons (2 cases), economic reasons (2 cases), dental treatment (3 cases), admission to a nursing home (2 cases), hospitalization for another disease (2 cases), transfer to another hospital (3 cases), according to exit interviews with physicians when applicable. Consequently, 13 patients continued therapy into year 3. Two osteoporotic vertebral fractures occurred during the first year, with none recorded during the second and third years. In the combination group, 16 cases dropped out (55.2%) unknown reasons (2 cases), economic reasons (1 case), dental treatment (2 cases), admission to a nursing home (2 cases), hospitalization for another disease (2 cases), transfer to another hospital (4 cases), and death (3 case) according to exit interviews with physicians when applicable. Consequently, 13 patients continued therapy into year 3. One osteoporotic nonvertebral fracture occurred during the first year, with none recorded during the second and third years.

4. Discussion

To our knowledge, this is the first report describing (1) direct comparative data between IBN alone versus IBN plus vitamin D, (2) adverse events, including fractures, and (3) compliance and discontinuation of IBN therapy over a long treatment period in Japanese postmenopausal osteoporosis patients. Combination therapy continuously and more significantly increased the percentage changes of L-BMD than did monotherapy over 36 months of treatment, suggesting that active vitamin D addition was required to maximize L-BMD gains during IBN usage. Both monotherapy and combination therapy groups exhibited relatively moderate compliance at 36 months (48.1% and 44.8%, respectively). We observed osteoporosis fractures in 2 of 13 monotherapy patients and 1 of 13 combination therapy patients, and no serious adverse effects occurred in either group. These findings suggest that IBN is a good option for the prolonged treatment of osteoporosis.

Ito et al. [10] recently described that femoral neck BMD increased by approximately 3.1% over 36 months of IBN plus active vitamin D treatment. On the other hand, Nakamura et al. [8] reported increases of L-BMD and H-BMD at 36 months of 9.0% and 3.1%, respectively. Our results showed that L-BMD and H-BMD respectively increased by up to 7.2% and 4.9% in the combination group over 36 months, which was comparable to or greater than the above reports [8,10]. The reason for this discrepancy is currently unknown, but it is conceivable that (1) during this study, we strongly and continuously advocated dietary improvement and appropriate exercise to all patients, and (2) the pretreatment H-BMD values in this cohort were considerably lower than those in the previous studies [8,10].

Long-term compliance is optimal for osteoporosis medication but is generally low [11]. Adherence to treatment is generally expressed as compliance [12]. Kishimoto et al. [13] reviewed that in Japan, compliance over 5 years was 20.8% and 60.9% for patients receiving BPs daily and weekly, respectively, with compliance over 1 year for daily, weekly, and monthly BP therapy of 38.6%, 70.6%, and 77.7% of patients. The authors also concluded that persistence, defined as the time to discontinuation, over 5 years was highest in patients receiving BPs on a monthly basis, in agreement with increased adherence to BP therapy in monthly than in daily and weekly regimens [13]. Our findings showed 3-year compliance to be 44.8%–48.1%, which was comparatively lower than Kishimoto's report [13], for the possible reason that 11 of the 30 (36.7%) cases were dropped out due to the admission to a nursing home and transfer to another hospital. Moving and death were largely inevitable, leaving unknown and economic reasons as the only avoidable true dropout causes. Avoidable true dropout cases were 4 of 14 (28.6%) in the monotherapy group and 3 of 16 (18.8%) in the combination group.

The main limitation of this study was its small sample size and no data of 25-hydroxyvitamin D values. Further studies are required to ascertain whether BMD increases continuously with IBN treatment and to what extent fractures and adverse effects can be prevented up to 5 years.

5. Conclusions

Combined therapy of IBN plus active vitamin D more significantly improved L-BMD than did IBN monotherapy for 3 years, with no serious adverse effects in either group. Thus, IBN plus active vitamin D represents an effective option for sustained osteoporosis treatment.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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