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Original Article

Comparison of effectiveness and safety of ibandronate and minodronate combined with eldecalcitol in primary osteoporosis of women: A 1-year follow-up study

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Abstract

Objectives: This is an open labeled and retrospective cohort study which compared the effectiveness and safety of ibandronate (IBN) and minodronate (MIN) combined with eldecalcitol (ELD) in primary osteoporosis of women.
Methods: One hundred and forty-eight primary osteoporotic women were classified into 3 groups; 1) intravenous IBN combined with oral ELD (IBN + ELD group, N = 50; 81.8 ± 6.2 years), 2) oral MIN combined with oral ELD (MIN + ELD group, N = 50; 77.2 ± 6.9 years) and 3) oral ELD alone (ELD group, N = 48; 75.0 ± 8.3 years). For statistical analysis, lumbar spine bone mineral density (L-BMD), hip total bone mineral density (H-BMD), serum corrected calcium (Ca), serum inorganic phosphorus (iP), intact-parathyroid hormone (PTH), tartrate-resistant acid phosphatase 5b (TRACP-5b), bone alkaline phosphatase (BAP), serum homocysteine (Hcy), estimated glomerular filtration rate (eGFR) and urine calcium / creatinine (Ca/Cr) ratio were measured until 12 months after the start of therapy.
Results: L-BMD values increased significantly in both IBN + ELD and MIN + ELD group, however, H-BMD increased significantly in the IBN + ELD group only. TRACP-5b values decreased rapidly during the first 6 months in both IBN + ELD and MIN + ELD group. However, BAP value in the IBN + ELD group decreased more gradually compared with that in the MIN + ELD group. Both serum Ca value and urine Ca/Cr ratio tended to increase, and the eGFR value decreased significantly in each group.
Conclusions: IBN combined with ELD administration can act more effectively to increase BMD compared with MIN combined with ELD administration. Differences of decreasing rate in TRACP-5b and BAP value may lead to differences of increased rate of BMD in the IBN + ELD and MIN + ELD group. Because many cases of osteoporosis are elderly persons associated with chronic kidney disease, monitoring of kidney function and concentration of Ca in blood and urine is essential.

Keywords: Eldecalcitol; Ibandronate; Minodronate; Osteoporosis

1. Introduction

Osteoporosis leads to reduced bone strength, which can increase risk of fracture. Since osteoporotic fractures are a health burden worldwide, identifying individuals at high risk of osteoporosis and preventing osteoporosis-related mortality and morbidity is a very important healthcare strategy. Bisphosphonates (BPs) are widely used in the treatment of

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osteoporosis to reduce the incidence of bone fractures [1]. However, an inherent constraint in the use of BPs is their poor bioavailability; oral intake leads to less than 1% absorption in the gut. In addition, the patient must not lie down for 30 min following oral BP administration due to the avoidance of topical effect of the BP tablet on the gastric mucosa and esophageal regurgitation of the tablet [2]. These drawbacks have led to reduced patient compliance and compromised treatment efficacy. Alternatively, ibandronate (IBN), a highly potent nitrogen-containing BP [3], can be infused intravenously, that enhances its bioavailability up to 100% and reduces administration frequency when compared with oral intake [4]. Intravenous IBN increased lumbar bone mineral density in patients with primary osteoporosis in the randomized, phase 3, double-blind MOVEST clinical trial [5]. Thus, intravenous IBN is expected to inhibit vertebral fractures. While, minodronate (MIN) developed in Japan is an oral BP containing nitrogen, which has a stronger inhibitory effect on farnesyl pyrophosphate synthase of osteoclasts compared with alendronate or risedronate [6]. MIN shows a potent depression effect on osteoclasts activities and inhibits bone absorption, resulting in accretion of bone mineral density (BMD). It is recommended to administer MIN combined with an active vitamin D_3 analogue in Japan [7]. Eldecalcitol (ELD), an active vitamin D_3 analogue, is frequently administered concurrently with other anti-osteoporotic drugs due to the effect in reducing the incidence of bone fractures in itself [8,9]. Furthermore, it is reported that the combination of IBN and ELD exerted a synergistic effect on BMD and inhibition of bone resorption [10]. To our knowledge, however, there have been no clinical reports on IBN or MIN and ELD combination therapy in osteoporotic patients to date. In the current study, we compared the effectiveness and safety of intravenous IBN and oral MIN when combined with oral ELD over a period of 12 months in primary osteoporosis of women.

2. Methods

One hundred and forty-eight primary osteoporotic women (mean age 78.3 ± 7.8 years) treated in our institutions between October 2013 and April 2015 enrolled in this 12-month investigation. Eligible participants were ambulatory women who met the criteria for osteoporosis as defined by the criteria of the Japanese Society for Bone and Mineral Research [7]; 1) presence of fragility fracture of either the lumbar spine or the proximal part of the femur, 2) other fragility fracture and a BMD of less than 80% of the young adult mean, 3) BMD of 70% or less or −2.5 standard deviations of the young adult mean with absence of fragility fracture. Patients who had a preexisting medical illness and were taking medications known to affect BMD or could not continue self-administration due to dementia and anoesia were also excluded. Additional exclusion criteria included any history of hemiplegia, ulcerative colitis, gastric resection, chemotherapy for cancer, ovarian resection, the intake of corticosteroid for collagen disease or pulmonary fibrosis, diabetes mellitus and thyroid disorder. The subjects were divided into three groups; patients underwent intravenous IBN treatment or oral MIN administration combined with ELD supplementation (IBN + ELD and MIN + ELD group, respectively) and administration of ELD alone as a control (ELD group). One of these three groups was assigned to one of three facilities without overlaps; the IBN + ELD group to Kawakita General Hospital, the MIN + ELD group to Shinshu University School of Medicine and the ELD group to Tokyo Women's Medical University. In the IBN + ELD group, there were 50 cases and they were administered IBN 1 mg/month intravenously combined with oral ELD 0.75 μg/day. Two patients had undergone BP therapy and 1 received alfacalcidol (ALF) for 1–2 years, however, these medications were discontinued for more than 1 year prior to the study. Twenty-two patients had a history of vertebral fracture, 11 of proximal femoral fracture and 4 of other fragile fracture, all of which had occurred over a year before the study. In the MIN + ELD group, there were 50 cases and they were administered oral MIN 50 mg/month combined with oral ELD 0.75 μg/day. Eight patients had undergone BP therapy and 1 received raloxifene for 1–2 years, however, these medications were discontinued for more than 1 year prior to the study. Twenty-four patients had a history of vertebral fracture, 4 of proximal femoral fracture and 1 of other fragile fracture, all of which had occurred over a year before the study. In the ELD group serving as the control group in this investigation, there were 48 cases and they received oral ELD 0.75 μg/day. One patient had taken raloxifene and 1 patient had taken BP therapy for 2 years over 1 year before the study. Twenty-four patients had a history of vertebral fracture, 2 of proximal femoral fracture and 2 of other fragile fracture, all of which had occurred over 1 year prior to the study. The patients in each group visited our hospital every month and had a medical checkup before taking an intravenous injection of IBN or getting the prescription.

For each group, we measured BMDs, lumbar spine (L2-4) BMD (L-BMD) and left total proximal femoral BMD (H-BMD), Ca/creatinine ratio in the urine (urine Ca/Cr) and intact parathyroid hormone (PTH) at the beginning of treatment and at 12 months after the start of therapy. BMDs were measured using dual-energy X-ray absorptiometry (DXA) (HOLOGIC Co., QDR4500, Tokyo, Japan). Patients with ectopic ossification in lumbar spine or proximal femur were excluded from the study. We also investigated tartrate-resistant acid phosphatase 5b (TRACP-5b), bone alkaline phosphatase (BAP), serum-corrected calcium (corrected Ca), serum phosphate (iP), serum homocysteine (Hcy) and estimated glomerular filtration rate (eGFR) before treatment and at 6 and 12 months after the commencement of therapy. For measurement of the bone turnover markers, TRACP-5b and BAP, Enzyme Immunoassay (DS Pharma Biomedical Co., Ltd., Osaka, Japan) and chemiluminescence enzyme immunoassay (Beckman Coulter, Inc., CA, USA) was used, respectively. The measured BMDs, TRACP-5b and BAP values were compared with the baseline value in each group. The changes over time of the values were expressed as percentage of the corresponding baseline value in each examination factor, which were termed the Δ% values and compared between the groups.

For the statistical comparison of the examined factors, such as age, L-BMD, H-BMD, serum corrected Ca, serum iP, intact-PTH, TRACP-5b, BAP, serum Hcy, eGFR and urine Ca/Cr ratio in the baseline between the three groups, Scheffe's F test was used. The Δ% L-BMD, Δ% H-BMD, Δ% TRACP-5b and Δ% BAP values between the three groups, Scheffe's F test was also used. The changes over time of the BMD value in each group was compared using a Wilcoxon signed-rank test. A p value of < 0.05 was considered to be statistically significant. The population variance among the Δ % values were compared using the Bartlett test. The existence of a difference in the population mean was determined using one-way analysis of variance (one-way ANOVA). Thereafter, the statistical significance between the BMDs and bone turnover markers was detected using the Pearson product–moment correlation coefficient ($p < 0.05$). Furthermore, the best-fit model was computed using a simple regression, which compared the parameters with a significant difference.

This study was approved by the institutional ethics review boards prior to its commencement and was conducted in accordance with the ethical tenets outlined in the 1964 Declaration of Helsinki for research involving human subjects. Written informed consent was obtained from all patients after detailed explanation of therapeutic agents.

3. Results

Baseline characteristics of patients in the IBN + ELD, MIN + ELD and ELD group are summarized in Table 1. The patients in the IBN + ELD group were older than those in the MIN + ELD and ELD group ($p < 0.05$ and $p < 0.01$, respectively). The L-BMD values in the IBN + ELD and MIN + ELD group were smaller than that in the ELD group ($p < 0.05$ and $p < 0.01$, respectively). The H-BMD value in the IBN + ELD group was smaller than that in the MIN + ELD and ELD group (each $p < 0.05$). The TRACP-5b value in the IBN + ELD group was larger than that in the ELD group ($p < 0.05$). The BAP value in the IBN + ELD group was larger than that in the MIN + ELD and ELD group ($p < 0.05$ and $p < 0.01$, respectively). These results suggest that bone metabolism of patients in the IBN + ELD group were turning over more rapidly than in the other groups, especially the ELD group. There were no significant differences in the other baseline values including Ca, iP, PTH, Hcy, eGFR and Ca/Cr between the groups at the study onset.

In the IBN + ELD group, 5 patients over 80 years dropped out due to 1 cardiac arrest, 1 renal failure, 1 spinal surgery for lumbar canal stenosis and 2 pneumonia. One patient dropped out from an unknown cause in the MIN + ELD group. There were no dropped out patients in the ELD group. As a result, 142 patients were included in final statistical analyses. No patient complained of any major acute phase response complication, such as fever or joint pain, nor were any fresh fragile fractures encountered in the study period. Hypercalcemia over 10.5 mg/dL of serum corrected Ca occurred in 2 cases in the IBN + ELD and ELD group, however, did not occur in the MIN + ELD group. In the 2 cases of hypercalcemia in the ELD group, the eGFR value was less than 30 ml/min/1.73 m^2 and their administration of ELD was discontinued after 12 months.

In the IBN + ELD group, average L-BMD and H-BMD values increased after 12 months compared with baseline values ($p < 0.01$ and $p < 0.05$, respectively) (Table 2). In the MIN + ELD group, L-BMD values increased after 12 months compared with baseline values ($p < 0.01$). However, BMD increased moderately in the ELD group and there were no significant differences in the L-BMD and H-BMD after 12 months. As a result, both Δ% L-BMD and H-BMD values after 12 months were larger in the IBN + ELD group compared with those in the ELD group ($p < 0.01$), and the Δ% L-BMD value after 12 months in the MIN + ELD group were larger compared with that in the ELD group ($p < 0.01$) (Fig. 1A and B).

Table 1
Baseline characteristics of patients in the groups.

Variable (unit)	IBN + ELD (N = 50)	MIN + ELD (N = 50)	ELD (N = 48)
Age (years)	69–92 (81.8 ± 6.2)*,**	63–85 (77.2 ± 6.9)*	56–88 (75.0 ± 8.3)**
L-BMD (g/cm^2)	0.623 ± 0.102**	0.678 ± 0.092*	0.765 ± 0.133**,*
H-BMD (g/cm^2)	0.500 ± 0.100**,**	0.584 ± 0.095**	0.634 ± 0.096**
Serum corrected Ca (mg/dL)	9.5 ± 0.3	9.3 ± 0.4	9.3 ± 0.3
Serum iP (mg/dL)	3.6 ± 0.5	3.6 ± 0.4	3.7 ± 0.5
Intact-PTH (pg/mL)	43.4 ± 16.1	37.6 ± 13.4	35.4 ± 19.7
TRACP-5b (mU/dL)	594.7 ± 294.7**	479.0 ± 206.4	366.6 ± 167.9**
BAP (U/L)	19.9 ± 9.5*,**	14.8 ± 7.2*	13.0 ± 4.7**
Serum Hcy (nmol/mL)	10.9 ± 4.0	10.6 ± 3.6	9.7 ± 3.1
eGFR (ml/min/1.73 m^2)	70.3 ± 18.9	70.3 ± 18.9	70.3 ± 17.7
Urine Ca/Cr ratio	0.21 ± 0.14	0.22 ± 0.15	0.20 ± 0.14
Past fractures	Vertebral fracture: 22 cases	Vertebral fracture: 24 cases	Vertebral fracture: 24 cases
	Proximal femoral fracture: 11 cases	Proximal femoral fracture: 4 cases	Proximal femoral fracture: 2 cases
	Other fragile fracture: 4 cases	Other fragile fracture: 1 case	Other fragile fracture: 2 cases
Pre-treatment	Bisphosphonates: 6 cases	Bisphosphonates: 8 cases	Bisphosphonates: 1 case
	Alfacalcidol: 1 case	Raloxifene: 1 case	Raloxifene: 1 case

Mean ± standard deviation (SD) *$p < 0.05$, **$p < 0.01$.
IBN, ibandronate; ELD, eldecalcitol; MIN, minodronate; L-BMD, lumbar spine bone mineral density; H-BMD, hip total bone mineral density; Ca, calcium; iP, inorganic phosphate; PTH, parathyroid hormone; TRACP-5b, tartrate-resistant acid phosphatase 5b; BAP, bone alkaline phosphatase; Hcy, homocysteine; eGFR, estimated glomerular filtration rate; Ca/Cr, calcium/creatinine.

Table 2
The changes over time of the BMD value.

Variable (unit)	IBN + ELD		MIN + ELD		ELD	
	0 M	12 M	0 M	12 M	0 M	12 M
L-BMD (g/cm^2)	0.623 ± 0.102	0.674 ± 0.093**	0.678 ± 0.092	0.722 ± 0.085**	0.765 ± 0.133	0.766 ± 0.116
H-BMD (g/cm^2)	0.500 ± 0.100	0.533 ± 0.099*	0.584 ± 0.095	0.594 ± 0.105	0.634 ± 0.096	0.638 ± 0.104

Mean ± SD * $p < 0.05$, **$p < 0.01$.
BMD, bone mineral density; IBN, ibandronate; ELD, eldecalcitol; MIN, minodronate; L-BMD, lumbar spine bone mineral density; H-BMD, hip total bone mineral density.

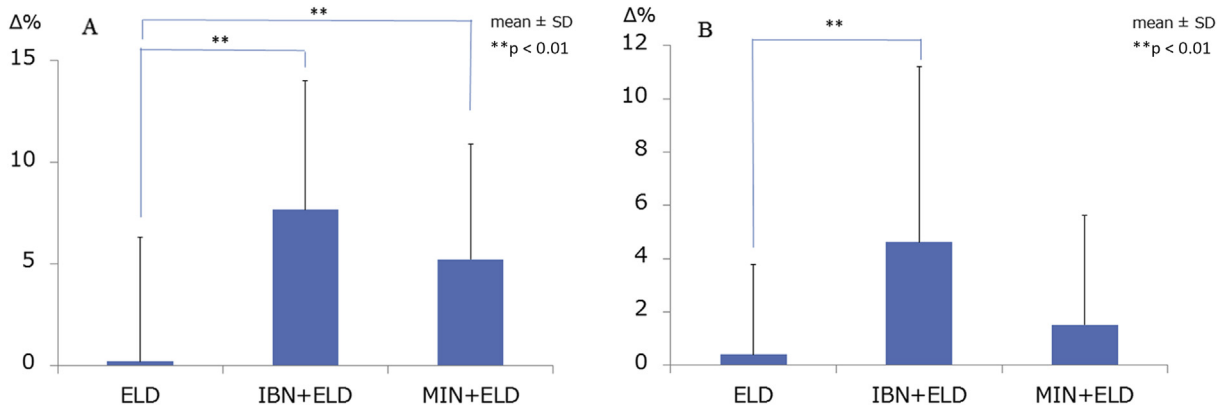

Fig. 1. A. Comparison of the Δ% L-BMD value after 12 months between the groups. The Δ% L-BMD value is significantly larger in the IBN + ELD and MIN + ELD group compared with that in the ELD group. **$p < 0.01$. B. Comparison of the Δ% H-BMD value after 12 months between the groups. The Δ% H-BMD value is significantly larger in the IBN + ELD group compared with that in the ELD group. **$p < 0.01$. ELD, eldecalcitol; IBN, ibandronate; MIN, minodronate; L-BMD, lumbar spine bone mineral density; H-BMD, hip total bone mineral density.

In all groups, TRACP-5b values decreased after 6 and 12 months compared with baseline values (each $p < 0.01$) (Table 3). BAP values in the IBN + ELD and MIN + ELD group, as well as ELD group, decreased after 6 and 12 months compared with baseline values ($p < 0.01$, $p < 0.01$ and $p < 0.05$, respectively). The Δ% TRACP-5b value decreased after 6 and 12 months in both IBN + ELD and MIN + ELD group compared with that in the ELD group (each $p < 0.01$) (Fig. 2A). The Δ% BAP value in the IBN + ELD decreased compared with that in the MIN + ELD and ELD group after 6 months ($p < 0.05$ and $p < 0.01$, respectively) and that in the ELD group after 12 months ($p < 0.01$) (Fig. 2B). It is noteworthy that the Δ% TRACP-5b value decreased very sharply during the first 6 months and then slowly in both the IBN + ELD and MIN + ELD group compared with that in the ELD group. The Δ% BAP value showed a similar decreasing pattern, however, decreased more gradually compared with the Δ% value of TRACP-5b. Both markers maintained within normal ranges through the treatment period. The Δ% L-BMD value negatively correlated with the Δ% TRACP-5b and Δ% BAP value (each $p < 0.01$) (Fig. 3A and B). The equations of these parameters were

$$Y = -1.908X - 28.093 \left(R^2 = 0.144\right), \quad \text{and } Y = -1.533X - 23.437 \left(R^2 = 0.150\right)$$

where Y is the Δ% TRACP-5b and Δ% BAP value (respectively), and X is the Δ% L-BMD value.

The Δ% H-BMD value negatively correlated with the Δ% BAP value ($p < 0.05$) (Fig. 3C). The equations of these parameters were

$$Y = -1.172X - 26.520 \left(R^2 = 0.063\right)$$

where Y is the Δ% BAP value and X is the Δ% H-BMD value.

The values for corrected Ca, iP, Hcy, eGFR, urine Ca/Cr and intact PTH in the groups are summarized in Table 4. There were no significant differences in the values for corrected Ca, iP and Hcy compared with the baseline values through the follow-up period in either group. However, the urine Ca/Cr ratio was higher ($p < 0.05$) and the PTH value was lower ($p < 0.01$) than that of baseline values after 12 months in the IBN + ELD group ($p < 0.05$). Moreover, the eGFR value after

Table 3
The changes over time of the TRACP-5b and BAP value.

Variable (unit)	0 M	6 M	12 M
TRACP-5b (mU/dL)			
IBN + ELD	594.7 ± 294.7	311.5 ± 170.0**	284.6 ± 121.8**
MIN + ELD	479.0 ± 206.4	234.6 ± 106.3**	210.8 ± 91.7**
ELD	366.6 ± 167.9	278.4 ± 116.5**	279.8 ± 130.2**
Serum BAP (U/L)			
IBN + ELD	19.9 ± 9.5	10.3 ± 5.0**	9.5 ± 2.7**
MIN + ELD	14.8 ± 7.2	9.1 ± 2.8**	8.7 ± 2.9**
ELD	13.0 ± 4.7	9.6 ± 3.0*	10.0 ± 3.1*

TRACP-5b, tartrate-resistant acid phosphatase 5b; BAP, bone alkaline phosphatase; M, month; IBN, ibandronate; ELD, eldecalcitol; MIN, minodronate.
Mean ± SD **$p < 0.01$, *$p < 0.05$.

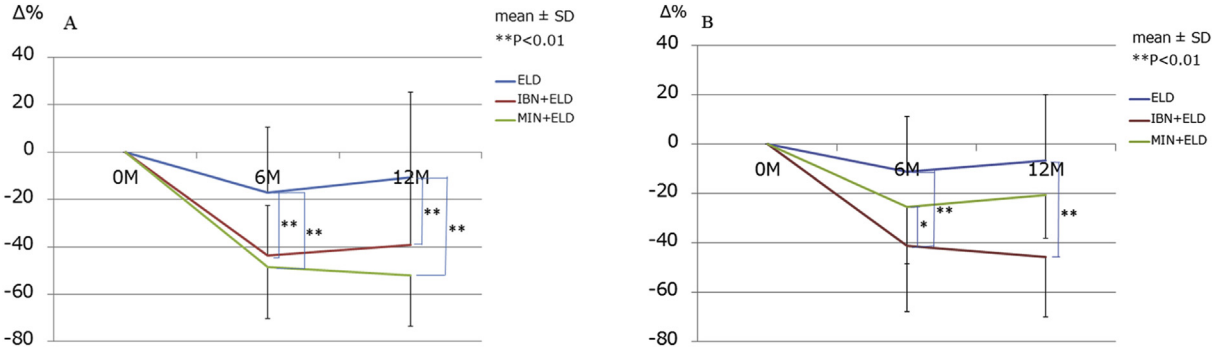

Fig. 2. A. The Δ% TRACP-5b value in the groups. The Δ% TRACP-5b value decreases significantly after 6 and 12 months in both IBN + ELD and MIN + ELD group compared with that in the ELD group. **p < 0.01. B. The Δ% BAP value in the groups. The Δ% BAP value in the IBN + ELD decreases significantly compared with that in the MIN + ELD and ELD group after 6 and that in the ELD group after12 months. **p < 0.01, *p < 0.05. TRACP-5b, tartrate-resistant acid phosphatase 5b; BAP, bone alkaline phosphatase.

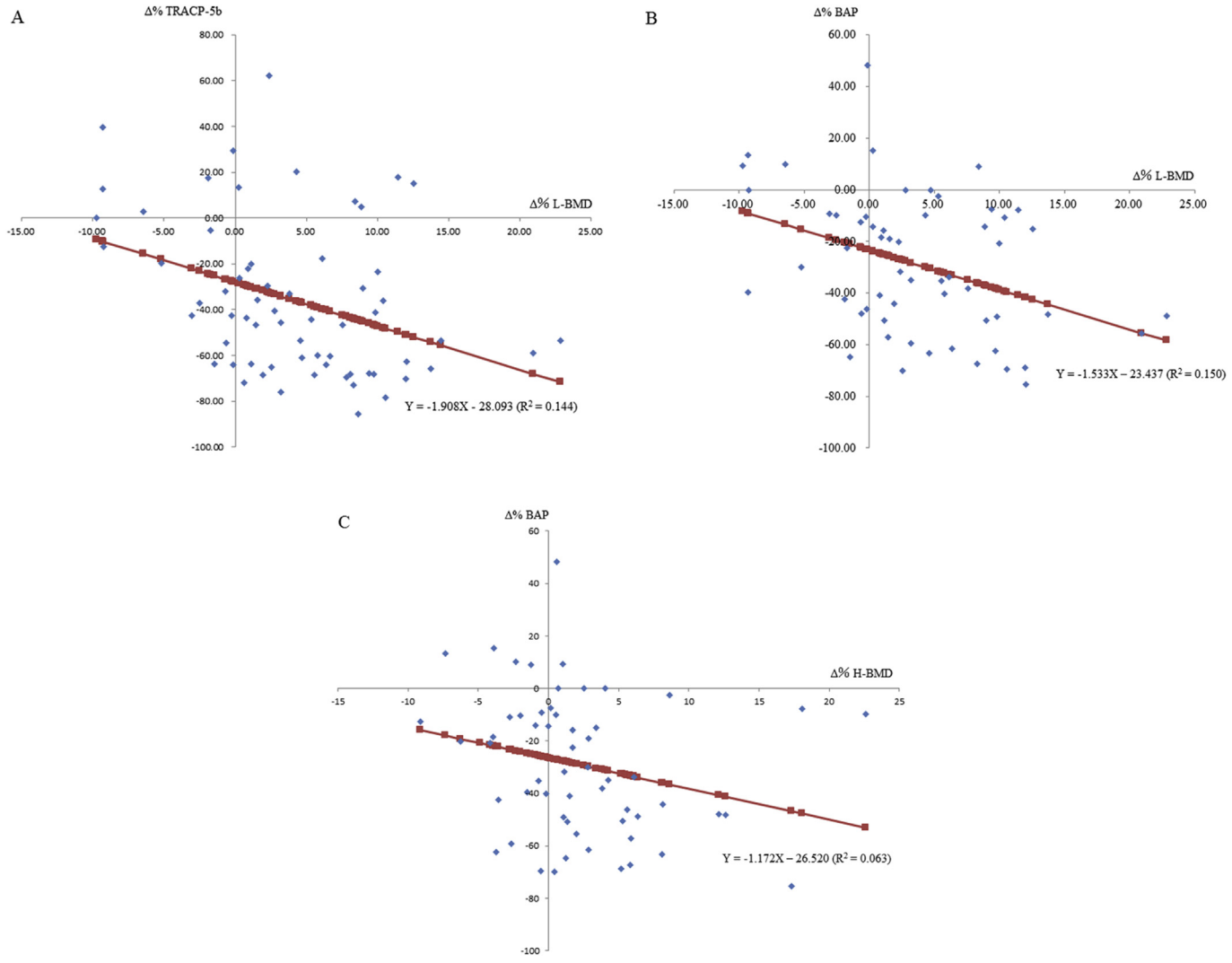

Fig. 3. A. Correlation between the Δ% L-BMD value and Δ% TRACP-5b value. There is a negative correlation between the Δ% L-BMD value and Δ% TRACP-5b value (p < 0.01). B. Correlation between the Δ% L-BMD value and Δ% BAP value. There is a negative correlation between the Δ% L-BMD value and Δ% BAP value (p < 0.01). C. Correlation between the Δ% H-BMD value and Δ% BAP value. There is a negative correlation between the Δ% H-BMD value and Δ% BAP value (p < 0.05). L-BMD, lumbar spine bone mineral density; TRACP-5b, tartrate-resistant acid phosphatase 5b; BAP, bone alkaline phosphatase; H-BMD, hip total bone mineral density.

Table 4
The changes over time of the Ca, iP, Hcy, eGFR, Urine Ca/Cr and PTH value.

Variable (unit)	0 M	6 M	12 M
Serum corrected Ca (mg/dL)			
IBN + ELD	9.5 ± 0.3	9.6 ± 0.4	9.6 ± 0.4
MIN + ELD	9.3 ± 0.4	9.3 ± 0.4	9.4 ± 0.4
ELD	9.3 ± 0.3	9.6 ± 0.5	9.5 ± 0.4
Serum iP (mg/dL)			
IBN + ELD	3.6 ± 0.5	3.7 ± 0.5	3.5 ± 0.4
MIN + ELD	3.6 ± 0.4	3.8 ± 0.4	3.5 ± 0.4
ELD	3.7 ± 0.5	3.8 ± 0.5	3.7 ± 0.4
Serum Hcy (nmol/mL)			
IBN + ELD	10.9 ± 4.0	11.8 ± 4.6	11.2 ± 2.7
MIN + ELD	10.6 ± 3.6	10.4 ± 3.8	10.6 ± 3.7
ELD	9.7 ± 3.1	11.0 ± 3.3	11.3 ± 3.6
eGFR (ml/min/1.73 m^2)			
IBN + ELD	70.3 ± 18.9	66.0 ± 14.3**	66.2 ± 14.3**
MIN + ELD	70.3 ± 18.9	70.1 ± 15.5	68.2 ± 13.4**
ELD	70.3 ± 17.7	66.3 ± 19.3*	64.0 ± 17.0**
Urine Ca/Cr ratio			
IBN + ELD	0.21 ± 0.14	–	0.30 ± 0.21*
MIN + ELD	0.22 ± 0.15	–	0.30 ± 0.18
ELD	0.20 ± 0.14	–	0.26 ± 0.18
Intact-PTH (pg/m^2)			
IBN + ELD	43.4 ± 16.1	–	36.3 ± 14.9**
MIN + ELD	37.6 ± 13.4	–	33.4 ± 16.7
ELD	35.4 ± 19.7	–	27.5 ± 12.8

Mean ± SD *$p < 0.05$, **$p < 0.01$.
Ca, calcium; iP, inorganic phosphate; Hcy, homocysteine; eGFR, estimated glomerular filtration rate; Ca/Cr, calcium/creatinine; PTH, parathyroid hormone; IBN, ibandronate; ELD, eldecalcitol; MIN, minodronate.

6 and 12 months were lower compared with the baseline value in the IBN + ELD group (each $p < 0.01$) and ELD group ($p < 0.05$ and $p < 0.01$, respectively), and that after 12 months was lower in the MIN + ELD group ($p < 0.01$).

4. Discussion

Since preventing fractures is the final target of osteoporosis management, the continuation of the treatment is very important. BPs have become a pillar of this aim, but oral BPs are accompanied by gastrointestinal problems and an immobility after internal use, those correspondingly decrease persistence rate [11]. However, persistence rate and adherence to BP treatment have increased in response to the lengthening of interval between doses, i.e., from daily to weekly and monthly regimen [12,13]. The persistence rate of therapy over a year in a monthly intravenous IBN was significantly greater compared with that in weekly ALN [14]. Therefore, both monthly IBN and MIN are expected to be beneficial particularly for elderly people. So far as we know, however, there are no previous clinical reports that demonstrated the combination effects of BIN or MIN and ELD. Hence, we addressed this major issue in this research.

One of major limitations of the present study is the difference of baseline characteristics of patients. The patients enrolled in this study were elderly at 78.3 years on average, and the patients in the IBN + ELD group were older than those in the MIN + ELD and ELD group. For this reason, there were significant differences in BMDs and bone metabolism markers in the groups. Because majority in the IBN + ELD group had past fractures and complications with daily medication, they had difficulty to make regular hospital visits to distantly-positioned academic medical centres where the MIN + ELD or ELD administration was assigned. Therefore, they presumably had no other choice to choose nearby general hospitals where the IBN + ELD administration was assigned for treatment of osteoporosis. Results of our research have suggested, however, that characteristic features of intravenous IBN including excellent absorption rate and releasing from cumbersome procedure for oral administration which results in low adherence have an advantage for such aged patients over oral MIN.

Since sufficiency of serum 25(OH)D is required to exert the effects of BPs, there are some reports that combined therapy of BPs and active vitamin D increased BMD and reduced fracture incidence. Co-administration of ALN and ALF significantly inhibited vertebral fracture in severe osteoporotic patients as compared with ALF-alone treated patients [15]. Combination ALN and ALF also increased L-BMD and H-BMD to a greater extent than either therapy alone [16]. Since Ca absorption from the intestine has decreased in the elderly person, BPs are combined with active vitamin D [15]. ELD is an analog of 1,25-dihydroxyvitamin D3. The 3-year randomized, double-blind, active comparator, superiority trial tested the efficacy of daily oral 0.75 μg ELD versus 1.0 μg ALF for prevention of osteoporotic fractures [8]. It was suggested that ELD for 3 years is associated with a lower risk of vertebral and wrist fractures, greater improvements in lumbar spine BMD, and greater decreases in bone turnover than ALF in vitamin D-sufficient patients with osteoporosis. Thus, ELD supplementation of BPs could be an effective treatment for both satisfying serum vitamin D requirements and prevention of hypocalcemia and acute-phase reactions [17]. In the present study, L-BMD value increased significantly after 12 months compared with baseline values in both IBN + ELD and MIN + ELD group, however, H-BMD increased significantly in the IBN + ELD group only. These results show that although both IBN and MIN are monthly regimen, characteristics of intravenous IBN may have an advantage for elderly patients over oral MIN as we expected when we designed a treatment protocol of this research. TRACP-5b values decreased rapidly during the first 6 months and thereafter slowly within normal range in both the IBN + ELD and MIN + ELD group. However, BAP value in the IBN + ELD group decreased more gradually compared with that in the MIN + ELD group until 12 months. These results suggest that intravenous IBN combined with oral ELD administration may inhibit the activity of osteoclasts and its coupling with osteoblasts more effectively compared with oral MIN combined with ELD administration. Considering that the changes over time of L-BMD value correlated negatively with those of TRACP-5b and BAP value, such differences of decreasing rate in TRACP-5b and BAP value may lead to differences of increased rate of BMD after treatment in the IBN + ELD and MIN + ELD group. Meanwhile, bone quality may be assessed by measuring bone matrix-related markers such as Hcy. It is

suggested that Hcy could be a surrogate marker for osteoporosis [18]. Therefore, we examined serum Hcy levels in the groups. Unfortunately, our study showed no significant differences in the Hcy level between the groups, which is comparable with other group's study which reported that IBN had no effect on the Hcy levels [19].

Because ELD has a longer half-life and stronger behavior to increase serum Ca level and inhibit bone absorption than other vitamin D analogues [20], hypercalcemia with concomitant increase in urinary Ca excretion is concerned as a side effect. Indeed, both serum and urinary Ca value tended to increase, and the eGFR value decreased significantly in each group in this study. These results suggest that ELD administration had negative effect on renal function of the elderly patients. Because the majority of participants in this trial were elderly, the baseline eGFR value in each group indicated grade II chronic kidney disease already. Therefore, significant decrease in eGFR with concomitant increase in serum Ca level and urinary Ca excretion may have developed by coadministration of ELD and BPs. Considering that the urine Ca/Cr rate was significantly higher and the PTH value was lower than that of baseline value after 12 months in the IBN + ELD group, there is a high possibility that this event occurred specifically to participants in the IBN + ELD group whose bone metabolism were turning over rapidly in the baseline. Attention needs to be paid to Ca metabolism in the case of combined administration of ELD and intravenous BPs. These results suggest that elderly persons who are easily lapsed into appetite loss and dehydration, which increases the load on the kidneys to accelerate the decline in renal function, are exposed to the risk of hypercalcemia and increase of Ca elimination in urine. Therefore, monitoring of kidney function and concentration of Ca in blood and urine may be necessary when BPs are administered with ELD.

5. Conclusions

We compared the effectiveness and safety of intravenous IBN and oral MIN when combined with oral ELD over a period of 12 months in primary osteoporosis of women. It is suggested that although both IBN and MIN are monthly regimen, characteristics of intravenous IBN may have an advantage for elderly patients over oral MIN and that intravenous IBN combined with oral ELD administration may inhibit the activity of osteoclasts and its coupling with osteoblasts more effectively compared with oral MIN combined with ELD administration. Monitoring of kidney function and concentration of Ca in blood and urine may be necessary when BPs are administered with ELD.

Conflict of interest

All named authors hereby declare that we have no conflict of interest to disclose.

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References

[1] Maraka S, Kennel KA. Bisphosphonates for the prevention and treatment of osteoporosis. BMJ 2015;351:h3783.
[2] Rakel A, Boucher A, Ste-Marie LG. Role of zoledronic acid in the prevention and treatment of osteoporosis. Clin Interv Aging 2011;6:89−99.
[3] Nakamura T, Nakano T, Ito M, Hagino H, Hashimoto J, Tobinai M, et al., MOVER Study Group. 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 2013;93:137−46.
[4] Inderjeeth CA, Glendenning P, Ratnagobal S, Inderjeeth DC, Ondhia C. Long-term efficacy, safety, and patient acceptability of ibandronate in the treatment of postmenopausal osteoporosis. Int J Womens Health 2014;7:7−17.
[5] Nakamura T, Ito M, Hashimoto J, Shinomiya K, Asao Y, Katsumata K, et al., MOVEST Study Group. Clinical efficacy and safety of monthly oral ibandronate 100 mg versus monthly intravenous ibandronate 1 mg in Japanese patients with primary osteoporosis. Osteoporos Int 2015;26:2685−93.
[6] Dunford JE, Thompson K, Coxon FP, Luckman SP, Hahn FM, Poulter CD, et al. Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. J Pharmacol Exp Ther 2001;296:235−42.
[7] Ebina K, Noguchi T, Hirao M, Kaneshiro S, Tsukamoto Y, Yoshikawa H. Comparison of the effects of 12 months of monthly minodronate monotherapy and monthly minodronate combination therapy with vitamin K2 or eldecalcitol in patients with primary osteoporosis. J Bone Miner Metab 2016;34:243−50.
[8] Matsumoto T, Ito M, Hayashi Y, Hirota T, Tanigawara Y, Sone T, et al. A new active vitamin D3 analog, eldecalcitol, prevents the risk of osteoporotic fractures-a randomized, active comparator, double-blind study. Bone 2011;49:605−12.
[9] Hagino H. Vitamin D3 analogs for the treatment of osteoporosis. Can J Physiol Pharmacol 2015;93:327−32.
[10] Sakai S, Takeda S, Sugimoto M, Shimizu M, Shimonaka Y, Yogo K, et al. Treatment with the combination of ibandronate plus eldecalcitol has a synergistic effect on inhibition of bone resorption without suppressing bone formation in ovariectomized rats. Bone 2015;81:449−58.
[11] Seo GH, Choi HJ. Oral bisphosphonate and risk of esophageal cancer: a nationwide claim study. J Bone Metab 2015;22:77−81.
[12] Makita K, Okano H, Furuya T, Urano T, Hirabayashi H, Kumakubo T, et al. Survey of the utility of once-monthly bisphosphonate treatment for improvement of medication adherence in osteoporosis patients in Japan. J Bone Miner Metab 2015;33:55−60.
[13] Confavreux CB, Canoui-Poitrine F, Schott AM, Ambrosi V, Tainturier V, Chapurlat RD, et al. Persistence at 1 year of oral antiosteoporotic drugs: a prespective study in a comprehensive health insurance database. Eur J Endocrinol 2012;166:735−41.
[14] Hadji P, Felsenberg D, Amling M, Hofbauer LC, Kandenwein JA, Kurth A. The non-interventional BonViva Intravenous versus Alendronate (VIVA) study: real-world adherence and persistence to medication, efficacy, and safety, in patients with postmenopausal osteoporosis. Osteoporos Int 2014;25:339−47.
[15] Orimo H, Nakamura T, Fukunaga M, Ohta H, Hosoi T, Uemura Y, et al. Effect of alendronate plus alfacalcidol in osteoporosis patients with a high risk of fracture. the Japanese Osteoporosis Intervention Trial (JOINT)-02. Curr Med Res Opin 2011;27:1273−84.
[16] Roux C, Binkley N, Boonen S, Kiel DP, Ralston SH, Reginster JY, et al. Vitamin D status and bone mineral density changes during alendronate treatment in postmenopausal osteoporosis. Calcif Tissue Int 2014;94:153−7.
[17] Srivastava T, Dai H, Haney CJ, Alon US. Serum 25-hydroxyvitamin D level and acute-phase reaction following initial intravenous bisphosphonate. JBMR 2011;26:437−8.

[18] Yang J, Hu X, Zhang Q, Cao H, Wang J, Liu B. Homocysteine level and risk of fracture: a meta-analysis and systematic review. Bone 2012;51:376–82.
[19] Tariq S, Tariq S, Alam SS, Baig M. Effect of ibandronate therapy on serum homocysteine and leptin in postmenopausal osteoporotic females. Osteoporos Int 2015;26:1187–92.
[20] Takeuchi Y. Current Topics on Vitamin D. Treatment of osteoporosis with eldecalcitol: its therapeutic efficacy and adverse effect on renal function. Clin Calcium 2015;25:425–32.