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Effects of 15 Years of Continuous Treatment with Bisphosphonate on Japanese Postmenopausal Osteoporosis Patients: An Observational Study

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Bisphosphonate (BP) is mainly used for the treatment of osteoporosis because of its efficacy in increasing bone mineral density (BMD) and reducing osteoporotic fractures. Previous large-scale studies indicated that continuous 10-year treatment with BP was effective for osteoporosis treatment. However, several studies indicated an increase in the risk of serious adverse events such as atypical femoral fracture on prolonged BP treatment. The benefits and risks associated with long-term BP therapy are controversial. On the other hand, the effects of BP for more than 10 years are unknown because of few previous studies. The aim of this study to investigate effects of continuous 15-year treatment with BP on Japanese postmenopausal osteoporosis patients. The study was a retrospective observational study. Fifteen of the 55 patients, who had already received a 10-year course of oral BP treatment in our previous study, continued the treatment for an additional 5 years. All patients made the choice additional BP treatment with informed consent. BMD; hip structural analysis (HSA); limbs-muscle volume; and serum total alkaline phosphatase, tartrate-resistant acid phosphatase-5b, calcium and phosphate levels were measured for 5 years in the 15 patients. BMD values at the lumbar spine were significantly increased at 15 years in comparison with that at 10 years. Section modulus of HSA for the intertrochanter was significantly increased at 15 years. No subsequent fractures or serious adverse events were observed. We demonstrated favorable effects of an additional 5 years of BP treatment in postmenopausal osteoporosis patients who had already received a continuous 10-year treatment.

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Introduction

Bisphosphonate (BP) is mainly used for the treatment of osteoporosis because of its significant efficacy in increasing bone mineral density (BMD) and reducing osteoporotic fractures. Several large-scale studies demonstrated that treatment with alendronate for 10 years resulted in a reduction in vertebral fractures and an increase in BMD, and decreased nonvertebral fractures in women whose femoral neck T score was –2.5 standard deviation or less, compared with the cessation of alendronate treatment after 5 years (Black et al. 2006; Adler et al. 2016). We also demonstrated that BMD at the lumbar spine was significantly and continuously increased by treatment with alendronate or risedronate over a period of 10 years without any AFFs, osteonecrosis of the jaw (ONJ) or other serious adverse events in 55 Japanese postmenopausal osteoporosis patients (Iba et al. 2020). In addition, the realistic comorbidity adjusted number needed to treat harm and number needed to prevent fragility fractures suggested that use of BP for more than 10 years remains favorable (Abrahamsen et al. 2016). However, effects of a continuous long-term treatment with BP for more than 10 years are unknown because of few previous studies. Then, we extended the investiga-

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tion undertaken in our previous study (Iba et al. 2020) by 5 years in the current study.

The absolute risk of serious adverse events such as atypical femoral fracture (AFF) is indicated to be higher in patients on prolonged BP therapy, with the risk decreased on discontinuation of the treatment. However, no cause-and-effect relationship has been established (Shane et al. 2014; Adams et al. 2018). Previous studies indicated that while there is no consensus on when to discontinue BP use or for how long, there seem to be a clinical benefit of a drug holiday with regard to AFF risk (Schilcher et al. 2015; Black et al. 2020). In addition, the preventive effect of BP on fragility fractures is indicated to last several years after cessation, whereas the risk of atypical fractures decreases rapidly (Schilcher et al. 2015). Another consideration for a long-term BP treatment is that the incidence of AFFs remains low in comparison with the number of potential osteoporotic fractures avoided (Black et al. 2020). Other studies also indicated that patients who are at high risk for osteoporotic fractures may benefit from more than 5 years, and up to 10 years of BP medication, although the optimal duration of that has not been determined (Bone et al. 2004; Qaseem et al. 2017; Siu et al. 2019). Thus, we should carefully weigh the risks and benefits associated with long-term BP therapy.

Evidence has accumulated regarding the effects of anabolic agents such as teriparatide or romosozumab on increasing bone mineral density and reducing the risk of fragility fracture (Neer et al. 2001; Saag et al. 2017; Hagino et al. 2021; Poutoglidou et al. 2022). On the other hand, the anabolic agents are considered a treatment of choice only for very high-risk osteoporosis patients. Therefore, we do not generally use these agents for the treatment of osteoporosis patients, and the administration period of these agents is limited to 1 or 2 years. In terms of planning for the long-term treatment of osteoporosis patients without very high-risk of fragility fractures for periods more than 10 years, we, therefore, consider the long-term use of anti-resorptive agents such as BP and denosumab, for which a good deal of evidence exists regarding their ability to prevent fragility fractures (Cranney et al. 2002; Wells et al. 2008; Orimo 2015; Papapoulos et al. 2015).

Moreover, Japanese osteoporosis patients are usually administrated with a half-dose of alendronate and risedronate in comparison with the patients in the US and Europe (EU), although the physical size of patients in Asian is generally smaller than that of Caucasians. Therefore, despite a number of studies on the efficacy and risks of long-term treatment with BP in the US and EU, we question whether all of the findings reported to date applies to Japanese osteoporosis patients (Ebetino et al. 2011). The aim of this study was to investigate the effects of a 15 years of treatment with BP on Japanese postmenopausal osteoporosis patients who had already received 10 years of continuous BP treatment.

Materials and Methods

Study designs

Subjects included 55 Japanese postmenopausal osteoporosis patients who received 10 years of continuous treatment with oral BP including oral alendronate (5 mg/day or 35 mg/week) or risedronate (2.5 mg/day, 17.5 mg/week or 75 mg/month) in the outpatient clinic of our hospital until December 2017 (Iba et al. 2020). Thirty-five of the 55 patients were excluded from the current study due to admission to other hospitals or other medical care facilities, interruption to their attendance at the clinic due to physical deterioration by aging, dementia, treatment for other malignant diseases, or death within the 5 years from 2017. All patients were informed of the benefits and risks of additional treatment with BP, and made the choice to additionally continue or discontinue BP treatment for 5 years, which is a 5-year extension of our previous study (Iba et al. 2020). Five patients did not want to further continue BP medication, and then continued treatment with only alfacalcidol or eldecalcitol.

Subjects

Fifteen postmenopausal osteoporosis patients, aged 69-89 years old, satisfied the following criteria: 1) Patients had received 10 years of continuously oral BP treatment, including alendronate (5 mg/day or 35 mg/week) in 8 patients and risedronate (2.5 mg/day or 17.5 mg/week) in 7 patients, with alfacalcidol (1.0 μg/day) or eldecalcitol (0.75 μg/day). 2) Their T-score was $-3.3 \leq \text{BMD} \leq -2.5$, or there was a history of a vertebral fracture before the start of the first 10-year BP treatment, which denote to be no very high-risk osteoporosis patients. 3) They had no disease such as hyperparathyroidism, Cushing's syndrome, rheumatoid arthritis, diabetes mellitus, or renal disease; and had not received glucocorticoids or other anti-osteoporosis agents according to their medical records. 4) All patients treated with BP were continuously and longitudinally evaluated and followed up by the author in the outpatient clinic of the university hospital for more than 15 years (Table 1).

Measurements

All data were retrospectively collected. The age; BMD at the lumbar spine (L1-L4), total hip, distal 1/10 and 1/3 of the radius; hip structural analysis (HSA); limbs-muscle volume (Lean, g) (Hologic Horizon-A, Marlborough, MA, USA); serum total alkaline phosphatase [(ALP, reference range 110-370 IU/l) measured using the Japan Society of Clinical Chemistry (JSCC) method, which was calculated from the values measured using International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) method from 2020], and serum tartrate-resistant acid phosphatase-5b (TRAP-5b, reference range 120-420 mU/dL), as bone metabolic markers; as well as serum calcium (Ca, reference range 8.4-10.4 mg/dl), which was corrected against serum albumin level, and serum phosphate (P,

Table 1. Demographic data in the patients after continuous treatment with bisphosphonate for 10 years.

Case	Age	Drug	previous fracture	BMD (g/cm^2)				HSA FN		HSA IT		HSA FS		Lean (g)	ALP (IU/l)	TRAP (mU/dL)	Ca (mg/dl)	P (mg/dl)	eGFR ($mL/min/1.73m^2$)
				lumbar	hip	1/10 R	1/3 R	SM	BR	SM	BR	SM	BR						
1	74	Aln		0.67	0.589	0.295	0.483	0.59	15.7	2.41	12.5	1.36	3.7	4.74	215	352	9	3.3	86.3
2	89	Aln	a vertebra	0.957	0.666	0.268	0.469	1.11	20	3.78	12.4	2.4	4	6.06	146	436	9.1	3.8	69.6
3	71	Aln		0.757	0.571	0.246	0.476	1.14	15.8	2.84	14	1.53	4.4	5.25	295	270	8.8	2.7	77.2
4	79	Ris	a vertebra	0.792	0.755	0.332	0.435	0.84	13.4	4.41	8.4	2.01	3.9	4.84	239	238	8.5	3.8	69.5
5	73	Aln		0.663	0.617	0.232	0.411	0.79	16.4	3.13	11.3	1.57	4.2	4.34	195	341	9.3	3.5	72.4
6	74	Ris		0.642	0.618	0.286	0.4	1.21	20.8	3.52	12.5	2	5.7	5.45	119	214	9.2	3	47.3
7	82	Aln	a vertebra	0.844	0.681	0.22	0.48	1.17	16.9	3.99	10.6	2.04	3.1	5.54	241	328	10.2	3.2	64.5
8	71	Aln		0.77	0.745	0.37	0.623	1.14	10.9	4.05	8.8	1.82	4	5.44	199	158	9.9	3.7	58
9	76	Ris		0.62	0.567	0.264	0.407	0.72	17.1	2.45	12.6	1.34	4.9	4.7	107	311	9.6	4.3	76.8
10	78	Ris		0.621	0.541	0.205	0.35	0.77	19.8	2.94	14.5	1.78	5.9	5.41	223	491	9	3.5	56.1
11	74	Ris		0.73	0.632	0.229	0.427	0.93	16.5	3.83	11.4	1.87	4	5.29	204	293	9.3	3.6	49.6
12	83	Aln		0.675	0.695	0.336	0.52	1.1	19.9	4.11	11.1	2.19	3.6	6.44	294	375	9.3	3.3	79.7
13	69	Ris		0.744	0.555	0.311	0.483	0.81	20.1	2.52	13.7	1.45	4.1	5.6	143	304	8.8	3.6	84.2
14	83	Aln		1.113	0.581	0.228	0.447	0.86	17.7	3.69	13.2	2.01	5.5	5.13	227	330	9	4	50.5
15	72	Ris	a vertebra	0.86	0.637	0.327	0.509	0.44	24.1	2.28	10.3	1.39	3.4	4.91	281	315	9.1	2.6	63.8

Patients had received 10 years of continuously oral alendronate (Aln) in 8 patients and risedronate (Ris) in 7 patients. Four patients had suffered a vertebral fracture before the start of the first 10-year treatment with BP (previous fractures). BMD at the lumbar spine (L1–L4, lumbar), total hip (hip), distal 1/10 and 1/3 of the radius (1/10R, 1/3R); hip structural analysis (HSA) at the femoral neck (FN), intertrochanter (IT) and femoral shaft (FS), Section modulus (SM) and buckling ratio (BR); limbs-muscle volume (Lean, g); serum total alkaline phosphatase (ALP); serum tartrate-resistant acid phosphatase-5b (TRAP-5b); serum calcium (Ca); serum phosphate (P); estimated glomerular filtration rate (eGFR)

reference range 2.5-4.5 mg/dl) levels were measured for 5 years after the start of additional treatment. Biochemical blood tests were performed to evaluate the adverse effects of bisphosphonate. Estimated glomerular filtration rate (eGFR, mL/min/1.73m^2) was calculated from the creatinine level for the assessment of renal function. Before and after the start of the additional 5 year-treatment of BP, renal failure was diagnosed on the basis of an eGFR value less than 35 mL/min/1.73m^2. BP was discontinued for the osteoporosis patients with renal failure. Limbs-muscle volume and HSA to capture bone structure in cross sections at the narrow femoral neck, intertrochanter and femoral shaft sites were measured by whole-body scan using the same machine as that for BMD measurement (Hologic Horizon-A, Marlborough, MA, USA), with the system software providing these values. Section modulus (cm^3) of HSA is an index of resistance to bending forces, and buckling ratio describes the stable configuration of thin-walled tubes subjected to compressive loads. Buckling ratio is presented only for the femoral neck and intertrochanter regions as this parameter is not important in the femoral shaft. The occurrence of new vertebral fracture was evaluated from thoracic and lumbar roentgenogram findings. In addition, we also investigated 5 patients who were only prescribed alfacalcidol (1.0 μg/day) or eldecalcitol (0.75 μg/day) during a 3-year period having discontinued BP medication after 10 years of continuous BP treatment.

Research ethics

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from the patients before enrollment in this study. The study was approved by the Institutional Review Board (No. 332-3191).

Statistical analysis

The results are expressed as mean ± S.D. Statistical analyses were performed using Paired *t* test for comparison between 10 and 15 years of treatments, and one-way repeated-measures ANOVA for evaluation of longitudinal changes. A *p* value of less than 0.05 was considered significant. All analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, version 1.54).

Results

BMD values at the lumbar spine at 15 years of BP treatment were significantly increased in comparison with those at 10 years of the treatment (Table 2). Section modulus of HSA for the intertrochanter at 15 years was significantly increased in comparison with that at 10 years (Table 2). BMD at the distal 1/10 of the radius showed a slight but significant decrease at 15 years (Table 2). On the other

Table 2. Comparison between 10 and 15 years of bisphosphonate treatment.

		10 years	15 years	*t* test
Age (years)		75.5 ± 5.7	81.5 ± 5.7	
BMD (g/cm2)	LS	0.761 ± 0.139	0.830 ± 0.196	0.0047*
	Hip	0.630 ± 0.067	0.621 ± 0.065	0.2714
	1/10 R	0.277 ± 0.050	0.262 ± 0.054	0.0057*
	1/3 R	0.461 ± 0.064	0.455 ± 0.070	0.1685
HSA				
SM (cm^3)	FN	0.91 ± 0.23	0.93 ± 0.25	0.5585
	IT	3.33 ± 0.72	3.52 ± 0.61	0.0220*
	FS	1.78 ± 0.33	1.76 ± 0.33	0.3916
BR	FN	17.67 ± 3.24	18.04 ± 3.37	0.5750
	IT	11.82 ± 1.79	11.85 ± 1.64	0.8342
Lean (g)		5.28 ± 0.54	5.26 ± 0.57	0.8528
BTM				
ALP (IU//l)		208.5 ± 59.4	197.7 ± 51.8	0.4052
TRAP-5b (mU/dL)		317.2 ± 85.5	341.1 ± 161.0	0.4797
Ca (mg/dl)		9.21 ± 0.43	9.25 ± 0.34	0.7753
P (mg/dl)		3.46 ± 0.46	3.54 ± 0.35	0.5348

BMD at the lumbar spine (LS) and section modulus (SM) of HAS of the intertrochanter (IT) at 15 years of treatment were significantly higher than at 10 years. BMD of the distal 1/10 of the radius (1/10 R) slightly decreased. There were no significant differences in BMD at the total hip (Hip) and the distal 1/3 of the radius (1/3 R), other HSA measurements, limbs-muscle volume (Lean), or bone turnover markers (BTM; ALP, TRAP-5b, Ca, P). Statistical analyses were performed using Paired t test for comparison between 10 and 15 years of treatments. A *p* value of less than 0.05 was significant*.

hand, no significant changes were observed in BMD at total hip or the distal 1/3 of the radius, other HSA measurements, limb-muscle volume, or bone turnover markers over the 5 years of the additional treatment (Table 2). No subsequent fragility fractures or serious adverse events including AFFs and ONJ were observed over the five-year period of continuous BP treatment. The eGFR values in all patients at 15 years were more than 45 mL/min/1.73 m^2 (mean value, 65.0 mL/min/1.73 m^2; range, 45.7-84.8 mL/min/1.73 m^2), which did not differ significantly from those at 10 years of the treatment (mean value, 67.0 mL/min/1.73 m^2; range, 47.3-86.3 mL/min/1.73 m^2). In terms of the longitudinal changes in BMD over the 5-year period, the BMD values at the lumbar spine were significantly increased from the initiation of the additional 5 years of BP treatment (Fig. 1). On the other hand, there were no significantly longitudinal changes in those at the total hip or at the distal 1/10 and 1/3 of the radius (Fig. 1).

Regarding the same parameters in the five patients who discontinued BP treatment after 10 years of continuous treatment, we did not find any significant changes in BMD values, HSA or bone turnover markers over the 3 years after BP discontinuation (Table 3).

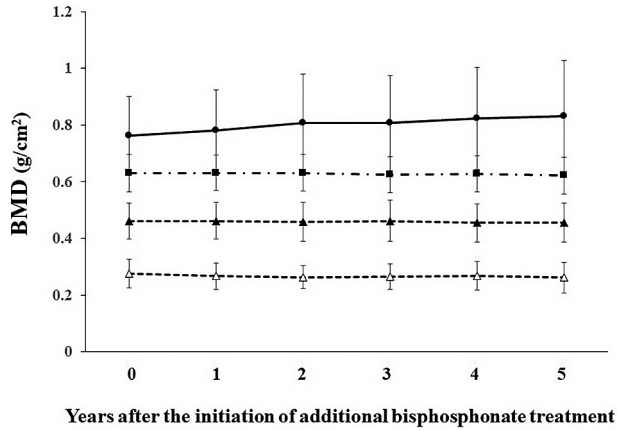

Fig. 1. Changes in BMD over the 5 years from the 10- to 15-year treatment with BP.
BMD at the lumbar spine (black circle) continuously and significantly increased over the 5 years (from 10- to 15-year treatment with BP). Longitudinal changes during 5-year period were evaluated by one-way repeated-measures ANOVA ($p < 0.0001$). BMD values at the total hip (black square), the distal 1/10 (white triangle) and the distal 1/3 (black triangle) of the radius showed no significant changes over the 5 years.

Discussion

Anti-resorptive agents are the mainstay of osteoporosis treatment because of their efficacy in increasing BMD and reducing osteoporotic fractures. However, the benefits and risks of long-term therapy with anti-resorptive agents are controversial (Shane et al. 2014; Adams et al. 2018). A number of studies have indicated an increase in AFF risk with the duration of BP treatment (Dell et al. 2012; Starr et al. 2018; Lo et al. 2019) as well as the clinically important benefits of a drug holiday with regard to significantly reducing AFF risk (Schilcher et al. 2011, 2015; Black et al.

Table 3. Changes of the parameters at 3 years after BP discontinuation in the patient who received 10-year BP treatment without additional continuation.

	At discontinuation	At 3 years after discontinuation	*t* test
Age (years)	81 ± 6.5	86 ± 6.5	
BMD (g/cm^2)			
LS	0.756 ± 0.111	0.770 ± 0.103	0.564
Hip	0.671 ± 0.079	0.667 ± 0.078	0.766
1/10 R	0.289 ± 0.052	0.275 ± 0.039	0.148
1/3 R	0.458 ± 0.038	0.460 ± 0.037	0.757
HSA			
SM (cm^3) FN	0.78 ± 0.04	0.83 ± 0.04	0.215
IT	3.19 ± 0.39	3.15 ± 0.51	0.832
FS	1.71 ± 0.13	1.70 ± 0.12	0.744
BR FN	15.36 ± 3.01	13.68 ± 1.11	0.269
IT	10.42 ± 2.1	10.42 ± 1.96	1.000
Lean (g)	6.08 ± 0.99	6.47 ± 1.47	0.180
BTM			
ALP (IU/l)	255.2 ± 68.7	233.8 ± 40.2	0.557
TRAP-5b (mU/dL)	427.4 ± 116.4	293.4 ± 91.2	0.108
Ca (mg/dl)	9.12 ± 0.43	9.24 ± 0.36	0.493
P (mg/dl)	3.4 ± 0.66	3.54 ± 0.4	0.581

There were no significant changes of BMD at the lumbar spine (LS), total hip (Hip) and the distal 1/10 (1/10 R) and1/3 (1/3 R) of the radius; hip structure analysis (HSA); limbs-muscle volume (Lean); or bone turnover markers (BTM) over 3 years after BP discontinuation. n = 5

2020). On the other hand, several studies have indicated the benefits of long-term BP medication from more than 5 years to more than 10 years for the treatment of the osteoporosis patients at high risk for fragility fractures beyond the rare incidence of AFF (Bone et al. 2004; Abrahamsen et al. 2016; Mahjoub et al. 2016; Qaseem et al. 2017; Wang et al. 2022). In this study, after 10 years of alendronate or risedronate treatment, we further continued treatment with those medications for 5 years in 15 of 55 osteoporosis patients. We found that BMD values at the lumbar spine were slightly but significantly increased over the 5 years of treatment, with no subsequent fractures or serious adverse events including AFFs and ONJ observed. With regard to the risks and benefits of 10 years of treatment with alendronate and risedronate, there is only limited evidence available (Black et al. 2006, 2012; Schwartz et al. 2010), and there are few reports on continuous BP treatment for more than 10 years. In addition, such evidence is based on the studies in mostly Caucasian postmenopausal women (Black et al. 2006, 2012; Schwartz et al. 2010). Furthermore, the previous study indicated that BPs with different dose regimens and pharmacodynamic properties may result in different risks and benefits in terms of the pharmacological treatment of osteoporosis (Ebetino et al. 2011). Despite a number of studies on the efficacy and risk of long-term treatment with BP, osteoporosis patients are administrated with a half-dose of alendronate and risedronate in Japan in comparison with the patients in the US and EU. A preceding pilot study in Japan indicates that 2.5 mg daily is as effective as a 10 mg dose in the US and EU in increasing the BMD at the lumbar spine, while bone turnover markers change more markedly and rapidly in the 10 mg group, and the incidence of adverse effects is higher in the 10 mg group. A dose-range finding study indicated that the optimal daily dose of alendronate is 5 mg for a Japanese population (Shiraki et al. 1999). This dose is half that used in Caucasians (10 mg/day). There is little information available regarding these factors in Japanese osteoporosis patients. We, therefore, believe that this study provides new information in terms of planning for the long-term treatment of Japanese postmenopausal osteoporosis patients over a period of 15 years, although it is the observational study in a small number of the patients.

The American Society for Bone and Mineral Research Task Force recommended a drug holiday after 5 years of oral BP or 3 years of intravenous BP. Meanwhile, it suggested the continuation of treatment for up to 10 years (oral) or 6 years (intravenous) with periodic evaluation and reassessment for the treatment of postmenopausal osteoporosis in high-risk patients including older women, those with a low hip T-score (≤ -2.5) or high fracture risk score, those with previous major osteoporotic fracture, or those who experienced fracture on therapy (Adler et al. 2016). In addition, the Task Force indicated that the risk of AFF, but not ONJ, clearly increases with BP therapy duration, but such rare events are outweighed by the reduction in the risk for vertebral fracture in high-risk patients (Adler et al. 2016). Furthermore, anabolic agents such as teriparatide and romosozumab, for which evidence exists regarding associated increases in bone mineral density and reduction in the risk of fragility fracture (Neer et al. 2001; Saag et al. 2017; Hagino et al. 2021; Poutoglidou et al. 2022), should be used for the treatment of very high-risk osteoporosis patients (Orimo 2015), and there is the limitation in terms of administration period as 1 or 2 years, even in the case of sequential therapy after both anti-resorptive and anabolic agents. Moreover, after long-term BP treatment, the role of switching to other effective treatments, such as denosumab, anabolic agents or other agents, remains controversial (Michalská et al. 2006; Bonnick et al. 2013; Bauer and Abrahamsen 2021). Regarding those recommendations, when we continue a long-term pharmacological treatment in osteoporosis patients with T-score for $-3.3 \leq \text{BMD} \leq -2.5$, or with just one vertebral fracture likewise the patients in the current study; we have only a few choices, and usually need to use antiresorptive agents such as BP or denosumab, because those patients need to treat with anti-osteoporotic drugs but do not have very high risk for subsequent fragility fractures.

Thus, considering long-term pharmacotherapy in real-world, we think that there are some osteoporosis patients who might need to be continuously treated with BP for more than 5 or 10 years. Especially, considering the treatment of Japanese osteoporosis patients, we need to make therapeutic strategy for more than 10 years regarding the aged society in Japan. Although there are few reports in terms of the effects of long-term BP treatment for a period of 15 years, we believe that the continuous use of alendronate and risedronate for more than 10 years with careful reassessment each year might be an option for the treatment of Japanese postmenopausal osteoporosis patients.

In this study, we also investigated changes after discontinuation of alendronate or risedronate treatment in five patients who had received 10 years of continuous BP treatment. Previous long-term studies have produced inconsistent findings, showing some loss of BP effect from 6 months to 5 years following discontinuation, as well as maintenance of some benefits in BMD, bone turnover markers, and nonvertebral fracture risk in other studies (Ensrud et al. 2004; Watts et al. 2008; Schwartz et al. 2010; Saag et al. 2021). The current study demonstrated no significant changes in BMD values, HSA or bone metabolic markers over 3 years after alendronate and risedronate discontinuation, although the sample size was very small and the observation period was only 3 years. These results might indicate the possibility that BMD values, HSA and bone turnover markers could be maintained for 3 years by treatment with only alfacalcidol or eldecalcitol. In other words, a drug holiday for 3 years might be feasible after 10-year continuous treatment with BP, although the additional alendronate and risedronate treatment increased the BMD values at the lumbar spine and section modulus of

HSA at the femoral intertrochanter.

For osteoporosis treatment in elderly patients, a previous study indicated that alendronate treatment reduces the risk of hip fracture with sustained safety (Axelsson et al. 2017). On the other hand, another study recommended close monitoring of kidney function in elderly patients due to the increased risk for acute kidney injury associated with BP use (Oda et al. 2022). We carefully assessed the renal function on the basis of an eGFR value and did not find any patients who experienced renal failure over the 15 years of treatment.

In this study, we investigated changes in HSA, which is a structural model for capturing bone structure in cross-section at the narrow femoral neck, intertrochanter and shaft sites to evaluate structural geometry and femoral strength (Beck 2007). We showed that the section modulus of HSA, which is an index of resistance to bending forces, at the intertrochanter was significantly increased at 15 years of BP treatment in comparison with that at 10 years of the treatment. We previously reported that the changing trends of the section modulus of HSA were different among the three sites. Especially, the apparent decline in section modulus at intertrochanter occurred after 70-74 years (Takada et al. 2007). In this study, 8 of 15 patients were younger than 75-year old (Table 1). Then, we speculate one of the reasons why the modulus only at intertrochanter increased by the BP treatment. In any case, these results suggested that the treatment with alendronate and risedronate for 5 years might increase femoral strength even after 10 years of continuous treatment with those agents. We believe that these results might provide new insights regarding the effect of continuous long-term treatment with alendronate and risedronate for more than 10 years, while the previously demonstrated significant effects of treatment with those agents in terms of improvement in the proximal femoral geometry in Japanese postmenopausal osteoporosis patients were observed within 1 year (Takada et al. 2011).

Recently, a population-based registry study of extended bisphosphonate use, which was a retrospective and observational cohort study from 1995 to 2018 in the US, reported that the early-user cohort (1998-2004) had 49.1% of patients on > 10 years of continuous BP therapy versus 34.6% in the later-user cohort (2005-2018) (Kline et al. 2023). The study suggested that many patients at high-risk for fracture have not continued BP medication due to lack of appropriate knowledge about the long-term benefits versus the very small risks. It also indicated an important issue that some patients stopped earlier than 10 years, despite being at high-risk for fracture and legitimate candidates for longer treatment (Kline et al. 2023). As the current observational study was based on the results of a small number of patients, further large-scale studies are needed to investigate real-world care concerning long-term BP treatment in Japanese osteoporosis patients.

There were several limitations to this study. First, the sample size of this study was small. We, therefore, could not draw any conclusions regarding the risk of serious medical adverse events including AFF and ONJ due to the 15-year treatment with BP. On the other hand, as a strong point in this study, we think that the same orthopaedic surgeon has continuously followed up all the osteoporosis patients during BP treatment for 15 years in the same outpatient clinic of our hospital. Second, we did not distinguish between the patients treated with alfacalcidol and eldecalcitol for data analysis. Third, medical laboratories in Japan utilize the JSCC method for blood ALP catalytic concentration measurement. However, the IFCC method is used worldwide for ALP catalytic concentration measurement. For global standardization, the JSCC method for ALP was switched to the IFCC method in medical laboratories in Japan in April 2020. Thus, the values for ALP in this study were calculated from the values measured using the IFCC method from April 2020. Fourth, during the 5-year period, we did not evaluate whether the grade of lumbar spondylosis and hip osteoarthritis progressed or not. Fifth, there was no control group for comparison between those with and without additional BP treatment in this study, although we showed changes of the same parameters in five patients who discontinued BP treatment after 10 years of continuous treatment. Sixth, we cannot necessarily generalize our findings because of a small sample size in the current study.

Conclusion

We investigated the effects of an additional 5 years of treatment with oral alendronate and risedronate on 15 postmenopausal osteoporosis patients who had already received 10 years of continuous those treatment. BMD at the lumbar spine and the section modulus of HSA for the intertrochanter significantly increased at 15 years of the treatment in comparison with that at 10 years, without any subsequent fragility fractures or serious adverse events including AFF and ONJ.

Author Contributions

All the named authors were actively involved in the planning, enactment and writing up of the study. Iba K. (manuscript preparation, coordination the study, treatment and assessment of clinical and radiographic findings); Hanaka M., Emori M. and Teramoto A. (evaluation of clinical and radiographic data and help in drafting manuscript); Takashima K., (statistical analysis and help in drafting manuscript); Takada J. (help in drafting manuscript).

Conflict of Interest

Kousuke Iba is an endowed chair in Department of Musculoskeletal Anti-aging Medicine, Sapporo Medical University. The donors of the endowed the department did not affect the content or interpretation of this manuscript. The other authors declare no conflict of interest.

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