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Original Article

Comparison of non-vertebral fracture between minodronate and risedronate therapy in elderly female patients with Alzheimer disease

Y. Sato[1], Y. Honda[1], J. Iwamoto[2], N. Amano[3]

[1]Department of Neurology, Mitate Hospital, 3237 Yugeta, Tagawa 826-0041, Japan; [2]Institute for Integrated Sports Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan; [3]Department of Food and Nutrition, Tezukayama University, 3-1-3 Gakuenmachi, Nara 631-8585, Japan

Abstract

Objectives: Minodronate is a nitrogen-containing bisphosphonate that is commercially available for the treatment of osteoporosis in Japan. Preclinical studies demonstrated that minodronate is at least 10 times more potent than alendronate in inhibiting bone resorption *in vivo*. A high incidence of fractures, particularly of the hip, represents an important problem in Alzheimer disease (AD) patients who are prone to falls and may have osteoporosis. **Methods:** A total of 256 elderly patients with AD were assigned to daily treatment with 1.0 mg of minodronate or a daily treatment with risedronate combined with daily 1000 IU ergocalciferol and 1200 mg elemental calcium, and followed up for 12 months. **Results:** At baseline, patients of both groups showed low 25-hydroxyvitamin D with compensatory hyperparathyroidism. Non-vertebral fractures occurred in 5 patients in the minodronate group and 7 patients in the risedronate group (5 hip fractures; one fracture each at the distal forearm and pelvis). There was no difference in risk of hip fracture between the two groups (p=.70; odds ratio=0.8). **Conclusions:** The study medications were well tolerated with relatively few adverse events and were equivalent in reducing the risk of a fracture in elderly patients with AD.

Keywords: Alzheimer Disease, Bone Mineral Density, Hip Fracture, Minodronate, Risedoronate

Introduction

Alzheimer's disease (AD) is a common neurodegenerative disorder characterized by progressive loss of memory and cognitive function. Also, advanced AD is associated with generalized weakness, high incidence of fractures, particularly of the hip[1-3]. This represents an important problem in AD patients, who are prone to falls4 and may have osteoporosis. Odds ratio of 6.9 has been reported for fracture prevalence between elderly persons with and without AD[4]. In addition, functional recovery after hip fracture in AD is poor[5-7], and patients with dementia have increased mortality during the 6 months after hip fracture[8]. The physical state of AD patients has increasingly become one of the critical issues in the management of such patients. Our previous study[9] demonstrated that deficiency of 25-hydroxyvitamin D (25-OHD) due to sunlight deprivation contributes to the reduced bone mineral density (BMD) in AD patients in nursing homes. Kipen et al.[10] examined demented women in the community and found that they have normal bone density, hypovitaminosis D and compensatory hyperparathyroidism. Recently, several reports indicated BMD is reduced in the earliest clinical stages of AD and associated with brain atrophy or hypothalamic volume and memory decline[11,12], while another cohort study showed low BMD and increased loss rate of BMD were associated with higher risk of AD[13].

Minodronate is a nitrogen-containing bisphosphonate that is approved by the Japanese ministry of health, labor and welfare for the treatment of osteoporosis. Preclinical studies demonstrated that minodronate is at least 10 times more potent than alendronate in inhibiting bone resorption *in vivo*[14,15]. A previous randomized, placebo controlled trial revealed that 0.5, 1.0 and 1.5 mg minodronate administered orally once a day

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Corresponding author: Dr. Yoshihiro Sato, Department of Neurology, Mitate Hospital, 3237 Yugeta, Tagawa 826-0041, Japan
E-mail: y-sato@ktarn.or.jp

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for 9 months to postmenopausal osteoporotic Japanese women increased the lumbar bone mineral density (L-BMD) by 4.93, 5.70, and 5.21% compared to the placebo group, respectively[16]. Because the incidence of adverse gastrointestinal events was 12.6, 6.3, and 11.1% with 0.5,1.0, and 1.5 mg minodronate, respectively, minodronate was shown to be a generally well-tolerated bisphophonate that is effective in increasing BMD. Another double blinded head to head trial of daily 1 mg minodronate and daily 5 mg alendronate for 12 months in Japanese women with postmenopausal osteoporosis showed similar changes in lumbar spine and total hip BMD after 12 months in both treatment groups[14]. Urinary deoxypyridinoline was significantly lower in the minodronate group than in the alendronate group at six months[17].

A randomized placebo-controlled double blind study about effect of daily oral minodronate on vertebral fractures was performed in 704 Japanese postmenopausal women with established osteoporosis for two years[18]. Minodronate treatment in that study reduced vertebral fractures by 59%. Minodronate therefore appears to be a promising new potent bisphosphonate for the treatment of osteoporosis.

So, we conducted a 1-year randomized open label trial to compare the efficacy of combined therapy with minodronate plus vitamin D2 and elemental calcium compared with once daily risedronate plus vitamin D2 and elemental calcium in reducing the severity of the osteoporosis and decreasing the risk of non-vertebral fractures in elderly female patients with AD. The rate of vertebral fractures was not determined in this study, because many vertebral fractures are asymptomatic among elderly AD patients and the interpretation of spinal x-ray films may be complicated by osteoarthritis or scoliosis.

Material and method

Study population

This study compared the incidence of non-vertebral fractures in the two groups of elderly female AD patients administered either daily minodronate or once daily risedronate combined with vitamin D and calcium. We recruited 256 ambulatory women from consecutive patients in our outpatient clinic who were more than 65 years old living in the community receiving care by their family caregivers and met criteria listed in the *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, Revised* for dementing disease and probable AD[19]. Patients were recruited from May 2010 to August 2010, and each patient was followed for 12 months. Patients younger than 65 years old were excluded from the study.

Patients with impairment of renal, cardiac, or thyroid function or those who had known causes of osteoporosis, such as primary hyperparathyroidism or renal osteodystrophy, were excluded from this study. Patients were excluded if they had been treated with corticosteroids, estrogens, calcitonin, bisphosphonate, calcium, vitamins D and K, serotonin re-uptake inhibitors, and proton pump inhibitors for 3 months or more during the 12 months preceding the study; and those who had been administered these agents for even a brief period during the preceding 3 months were also excluded. However, patients who taking drugs which may affect BMD such as acetylcholinesterase inhibitor (AChEI;i.e., donepezil[20]), antihypertensive drugs[21], or antiepileptics were included. Totally disabled AD patients were excluded, because their conditions virtually predicted minimum chance of fracture. Patients with a previous history of non-vertebral fracture were also excluded.

At baseline, we assessed body mass index (BMI) and illness duration. The Mini-Mental State Examination (MMSE)[22] was given to the patients, and activities of daily living (ADL) were assessed by the Barthel index (BI), in which a functional dependence score of 100 represents independence[23]. Sunlight exposure during the preceding year was assessed by the patients or family members and graded as almost none, less than 15 min per week, or longer[24]. Falls were defined as incidents where the subject fell, due to an unexpected loss of balance; patients who fell at least once in the 3 months before recruitment were defined as "fallers." The number of falls per subject was also recorded during the 1-year follow-up period.

Study protocol

All patients were informed of the nature of the study. Consent was obtained from each participant, or from family members when patients were unable to understand because of dementia. The study protocol was approved by the ethics committee of Mitate Hospital.

The AD patients were assigned, by means of computer-assisted random numbering, either to the treated group with minodronate and ergocalciferol (n=128) or daily risedronate and ergocalciferol (n=128). Patients in the minodronate group received a daily dose of 1.0 mg minodronate in a tablet (Bonoteo; Astellas Pharma Inc, Tokyo, Japan) and 1000 IU ergocalciferol and 1200 mg elemental calcium after breakfast. The risedronate group received a daily risedronate (2.5 mg/day) and 1000 IU ergocalciferol and 1200 mg elemental calcium. Patients were instructed to take the tablet with a cup of water (180 ml), 30 to 60 minutes before breakfast, and to remain sitting or maintain an upright position for 60 minutes thereafter. Adherence to study medication was assessed by counting the returned tablets. No dose adjustments were made at any time during the study. Patients were prohibited from taking any other drugs that could affect bone metabolism during the study period, excepting for those whom it was decided really necessary for accompanying conditions: i.e. antiepileptics, antihypertensive drugs, or corticosteroids. No placebo capsules were administered. No dose adjustments were made at any time during the study. Follow-up assessment of patients' condition was performed by physicians who did not participate in the initial randomization. Both groups were observed for 12 months. The patients' clinical status was assessed at baseline and all of them were followed every 4 weeks in the outpatient clinic, at which times non-vertebral fractures were recorded. Symptomatic non-vertebral fractures confirmed by radiological examinations were considered adverse clinical events, with no attempt to exclude fractures related primarily to trauma. Falls were registered by means of monthly "fall calendars".

Characteristic	Risedronate group (*n*=128)	Minodronate group (*n*=128)	*P* value*
Age (years)	72.4±4.1	71.9±6.1	.67
Duration of illness (years)	3.1±1.3	3.3±1.0	.71
Mini-Mental State Examination	22.3±3.1	21.5±2.8	.83
Interval since menopause (years)	17.2±6.2	16.4±7.3	.61
Barthel index†	89±7	91±9	.59
Body mass index (kg/m²)	19.9±3.4	19.5±4.2	.63
Faller (%)	42 (33%)	38 (30%)	.70‡
Sunlight exposure/week			
>15 min	13 (10%)	7 (4%)	
<15 min	20 (16%)	22 (17%)	
None	95 (74%)	99 (77%)	.37‡
Bone mineral density (BMD) (mmAL)	1.93±0.38	1.94±0.40	.78
Patients who taking drugs affecting BMD (%)			
Donepezil	98 (77%)	106 (83%)	.68
Antihypertensive drugs	32 (25%)	25 (19%)	.84
Antiepileptics	5 (4%)	4 (3%)	.56

*Values are mean±SD. *Unpaired t test; †ADL was evaluated by the Barthel index[23]; ‡Fisher's exact test. The reference range: bone mineral density, 2.19 to 2.91 mm Al.*

Table 1. Demographic and baseline clinical characteristics of the female patients with Alzheimer's disease at study entry.

The family members of participants were instructed to complete the calendar daily, marking an 'X' for each fall on the date that the fall occurred. In addition, the characteristics of each fall were written according to the timing, direction, and severity of a fall; and the activity in which a fall occurred and injuries due to a fall were also recorded.

Both groups were observed for 12 months. General medical evaluation, metacarpal BMD measurement, and laboratory values were assessed on entry and after 6 and 12 months later.

Metacarpal BMD measurements and laboratory values were assessed upon study entry to obtain baseline values. Computed X-ray densitometry (CXD; Teijin Diagnostics, Tokyo)[25] employing an improved microdensitometric method was used to quantify BMD in the left second metacarpal of each patient as described previously[26]. The computer algorithm for CXD compares bone radiodensity with the gradations of an aluminum step wedge, calculating bone thickness as an aluminum equivalent (mm Al) showing the same X-ray absorption. The validity and accuracy of this method have been described elsewhere[26].

In the morning of the day of bone evaluation, blood and urine samples were obtained from the 256 patients after an overnight fast. Blood samples were analyzed for ionized calcium, intact parathyroid hormone (PTH), and 25-OHD. Ionized calcium concentration was determined in fresh serum processed under anaerobic conditions using an ion-selective electrode and an ionized calcium analyzer (Jokoh, Tokyo, Japan). Serum PTH concentration was measured by an immunoradiometric assay (Sumitomo Biomedical, Osaka, Japan). Serum 25-OHD concentration was determined by radioimmunoassay (DiaSorin, Stillwater, MI). The normal ranges of the BMD and biochemical indices in elderly women are described in Table 2[27,28].

Study end points and statistical analysis

The sample size was based on an expected non-vertebral fracture incidence at 10% in both groups over 12 months. Assuming a 10% dropout rate over 12 months, the study had at least 90% power to detect a 60% reduction in fracture risk with a two-sided α=0.05 significance level.

The primary end point was defined as the incidence of a non-fracture. Values are given as the mean ± SD unless otherwise indicated. The difference in the incidence of fracture between the two patient groups during the 12 months follow-up was tested by chi-square test. The within-group changes from the baseline values were assessed by paired *t* test. Group differences of the categorical data were tested by Fisher's exact test. Spearman's rank correlation coefficients were calculated to determine the relationships between BMD and serum 25-OHD or intact PTH. BMD and laboratory values were expressed as a percent change from the baseline, and the two groups were compared by the Wilcoxon rank sum test. *P* values less than 5% were considered statistically significant.

Results

Baseline characteristics of study subjects (Tables 1 and 2)

Eight patients in the minodronate group and 12 in the risedronate group dropped out or withdrew from the study due to noncompliance, loss to follow-up, or intercurrent illness. Thus, a total of 236 patients (120 in the minodronate group and 116 in the risedronate group) completed the trial.

Table 1 lists the baseline characteristics of the participants. There was no significant difference between the two groups in duration of illness, MMSE, BI, BMI, BMD, and numbers of

Biochemical indices and group	Baseline	Follow-up	
		6 mo	12 mo
Faller (%)			
Minodronate group	38 (30%)*	24 (19%)*†	17 (13%)*†
Risedronate group	42 (33%)	21(16%)†	15 (12%)†
Ionized calcium (mEq/L)			
Minodronate group	2.39±0.18*	2.47±0.14*†	2.48±0.12*†
Risedronate group	2.40±0.16	2.45±0.11†	2.44±0.13†
Intact parathyroid hormone (pg/mL)			
Minodronate group	72.6±13.7*	37.2±10.4*†	32.5±5.4*†
Risedronate group	69.1±18.5	39.7±9.5†	30.8±8.2†
25-hydroxyvitamin D (ng/mL)			
Minodronate group	10.6±4.1*	20.8±5.3*†	24.5±4.1*†
Risedronate group	11.2±5.0	19.8±6.2*†	24.1±3.9*†

*Values are mean±SD. *P: not significant vs. risedronate group. †P<.01 for the comparison with the baseline value.*
Patients who fell at least once in the 3 months before recruitment or study period were defined as "fallers". The reference range of healthy elderly women: ionized calcium, 2.44 to 2.60 mEq/L; Intact parathyroid hormone, 35 to 52 pg/mL; 25-hydroxyvitamin D, 18.9 to 24.9 ng/mL[27,28].

Table 2. Falls and biochemical tests in the minodronate and risedronate groups at baseline and after 6, 12 months of follow-up.

fallers or patients who were taking drugs affecting BMD such as donepezil, antihypertensive drugs, or antiepileptics. BMI was low in both groups. Many of the patients in both groups had been exposed to sunlight less than 15 min a week because of being homebound. The average values of metacarpal BMD in the two groups were lower as compared to the reference range of normal Japanese population[27,28].

As shown in Table 2, in the two groups, the baseline values of serum ionized calcium, 25-OHD concentrations were low, while serum PTH was high as compared to the reference range of normal Japanese population[27,28].

When both patient groups were analyzed together, the BMD correlated positively with BMI (r=0.157, $p<.02$), and 25-OHD (r=0.307, $p<.0001$) concentrations, while BMD correlated negatively with PTH (r=-0.261, $p<.0001$). There were negative correlations between serum 25-OHD and PTH (r=-0.294, $p<.0001$) suggesting the existence of compensatory hyperparathyroidism.

During the study period, patients who received additional medications which may affect BMD in the minodronate and risedronate groups included two and three with antiepileptics ($p=.87$), four and six with antihypertensive drugs ($p=.74$), or 0 and one with corticosteroids ($p=.69$).

Fracture incidence

Non-vertebral fractures occurred in 5 patients in the minodronate group (4 hip fractures; one fracture at the proximal humerus) and 7 patients in the risedronate group (5 with hip fractures; one fracture each at the distal forearm and pelvis).

Hip fractures. There were 4 hip fractures in the minodronate group and 5 in the risedronate group. The odds ratio for hip fractures in the minodronate group and risedronate group was 0.8 (95% confidence interval [CI], 0.2 to 2.9; $p=.51$).

All fractures. There were 5 non-vertebral fractures in the treatment group and 7 in the control group. The odds ratio for all fractures in the minodronate group and risedronate group was 0.7 (95% CI, 0.2 to 2.2; $p=.61$).

Table 2 summarizes time-dependent changes in the frequency of fallers, i.e. those who had fallen at least once in 3 months. The numbers of fallers after 6 and 12 months, in the two groups, were significantly smaller as compared to the baseline number in each group ($P<.01$). There was no significant difference between the two groups in the number of falls per subject during the 12 months (2.1±0.6 in the minodronate group and 2.0±1.1 in the risedronate group).

Bone changes and blood biochemical markers

Figure 1 shows the percent changes from the baseline in metacarpal BMD during the 12 months. The percent changes in BMD were +2.5±0.3 in the minodronate group and +2.7±0.2 in the risedronate group. The difference between the two groups was not statistically significant ($p=.65$).

Changes in various parameters during the 12-month study period are summarized in Table 2. In both groups, serum calcium and 25-OHD increased significantly as compared to baseline value, and serum PTH decreased significantly as compared to baseline value in both groups. These changes were not significant between the two groups.

Adverse effects

Serious adverse events including death, overdose and any other event that was life-threatening or permanently disabling, or that required intervention to prevent permanent impairment were not observed in both groups. In the minodronate group, two patients experienced heartburn and one patients experienced abdominal pain, which eventually disappeared with ap-

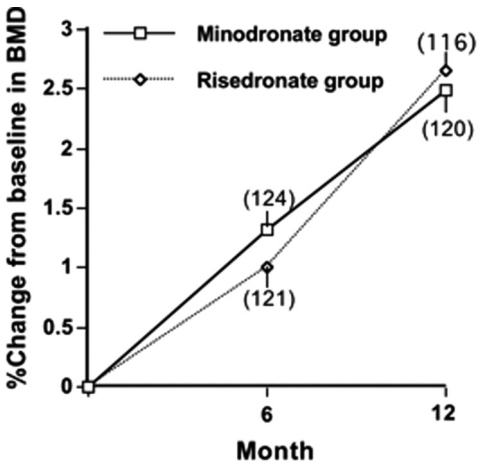

Figure 1. Percent changes (mean±SE) from baseline in metacarpal bone mineral density (BMD) after 6 and 12 months in the two groups of patients. During the 12 months, the differences in the percent changes in the BMD among the two groups were not statistically significant (based on Wilcoxon rank sum test; p=.88). Numbers in parentheses are the numbers of the subjects follow.

propriate therapy without discontinuation of the treatment. Three patients in the risedronate group experienced gastrointestinal symptoms such as heartburn and nausea, which eventually disappeared with appropriate therapy without discontinuation of the treatment.

Discussion

Metacarpal CXD measurement has been validated and its accuracy was found comparable to the better-known but less-available method of dual energy X-ray absorptiometry[29].

The present study was the first open label clinical trial comparing the incidence of non-vertebral fracture in subjects receiving daily minodronate 1.0 mg and daily risedronate therapy. Because preclinical studies demonstrated that minodronate is at least 10 times more potent than alendronate in inhibiting bone resorption *in vivo*[14,15], we anticipated the incidence of non-vertebral fracture is lower in the minodronate group than those of risedronate group. However the incidence of vertebral-fracture was equivalent in the two groups. Indeed, similar gains in metacalpal BMD was seen with daily minodronate 1.0 mg as compared daily risedronate 2.5 mg. As there were no significant differences in the number of the patients who were taking drugs affecting BMD such as donepezil, antihypertensive drugs or antiepileptics at baseline, these medications did not appear to contribute to significant gain of BMD or fracture incidence in the two groups. However, recent study suggested that use of AChEIs donepezil and rivastigmine is associated with a reduced risk of hip fractures in AD patients[20]. The fact that the number of subjects studied and the number of non-vertebral fractures was very small limits the ability to observe differences between treatment groups. Additionally, as many patients received donepezil, the differences in treatment effects between the two bisphosphonates might have been masked. Since there is no information about the influence AChEIs upon hip fracture during study period, thus is study limitation.

Previously, we showed non-vertebral fractures occurred in 27 patients (19 hip fractures) in the placebo group and 8 patients (5 hip fractures) in the risedronate group in randomized control trial in elderly women with AD[30]. The relative risk in the risedronate group as compared with the placebo group was 0.30 (95% CI, 0.14 to 0.64)[30]. A similar effect may be expected for inhibition of non-vertebral fracture in the minodronate group in randomized controlled trial of elderly female patients with AD. In addition, there was no difference in upper gastrointestinal tolerability.

In the study[30], randomized controlled trial of the treatment with risedronate and vitamin D2 may be effective in reducing the risk of a non-vertebral fracture in elderly female AD patients, the number of falls during the follow-up period was similar and reduced as compared to baseline values in the two groups, indicating vitamin D2 may have prevented falls in both groups. A recent study suggested that vitamin D supplementation reduces the risk of falls among ambulatory or institutionalized older individuals[31]. This implies that the frequency of fractures due to falls in AD patients is related to hypovitaminosis D.

Tanaka et al.[32] examined the effect of minodronate on BMD, bone turnover, bone histomorphometry and bone strength in ovariectomized (OVX) rats. Minodronate was administered orally once a day for 12 months at doses of 0, 0.006, 0.03 and 0.15 mg/kg from 3 months after OVX. Minodronate dose-dependently inhibited the decrease in BMD of lumbar vertebrae and femur. In the femur, treatment with 0.15 mg/kg minodronate increased the BMD of distal and mid sites to sham levels. In contrast, % changes of the metacarpal BMDs during 12 months in both minodronate and risedronate groups were similarly between 2.5% and 3.0% in the present study. The difference may be attribute to different effect of minodronate on spongy bone and cortical bone; i.e. it is possible that minodronate has stronger effect of increase BMD upon spongy bone than cortical bone. Indeed, Yoshida et al.[33] examined responses of trabecular and cortical bone mass and strength to minodronate in ovariohysterectomized Beagles with calcium restriction, and they concluded the cortical bone appeared to be less sensitive to the agent than the trabecular bone in the animal model.

This prospective comparison might be limited by its relatively small sample size. Non-vertebral fractures are infrequent clinical events; therefore, clinical studies comparing the efficacy between medications regarding the prevention of non-vertebral fractures normally require very large study samples (e.g., the estimated sample size would be approximately 2,300 per arm, which is required to detect the difference in fracture risk reduction between minodronate and risedronate seen in this study). Despite the limitation, the present study demonstrated

that minodronate may be associated with similar or superior efficacy to that of risedronate in reducing non-vertebral fractures in elderly female patients with AD, which should be further addressed in future studies involving larger study samples.

We conclude that female AD patients with low serum vitamin D with high bone remodeling due to compensatory hyperparathyroidism are at increased risk for non-vertebral fractures, particularly in the hip. Therapeutically in the risedronate group, combined treatment with minodronate, ergocalciferol and calcium may be safe and effective in increasing bone mass and reducing the risk of fractures in elderly women with AD.

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