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Zoledronic acid increases bone mineral density and improves health-related quality of life over two years of treatment in Chinese women with postmenopausal osteoporosis

Kwas zoledronowy stosowany przez dwa lata u Chinek z osteoporozą pomenopauzalną zwiększa gęstość mineralną tkanki kostnej i poprawia jakość życia związaną ze stanem zdrowia

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Abstract

Introduction: Osteoporosis is characterised by decreased bone mass and weakened bones, with an increased risk of fractures. Osteoporotic fracture, the most serious complication of osteoporosis, is related not only to lower bone mineral density (BMD), but also falls. Osteoporosis and fractures are associated with a decreased health-related quality of life (HRQL). Zoledronic acid (ZOL) is an intravenous once-yearly bisphosphonate that has been shown to be effective and safe in improving BMD and reducing fracture risk in controlled clinical trials.

Material and methods: In this self-controlled, prospective trial, 220 postmenopausal women with osteoporosis (mean age 67 years) received a single infusion of ZOL 5 mg at baseline and month 12. BMD, HRQL and Fall Index (FI) were measured at baseline, and months 12 and 24 (before each use of ZOL). The main outcome measures were the changes in lumbar spine and hip BMD and the changes in HRQL, the Short Form-36 questionnaire (SF-36). Additional comparisons were based on the FI. LSD multiple comparisons were used in the comparisons of BMD, SF-36 domain scores and FI.

Results: The patients had significantly higher L1-4, total hip, femoral neck and trochanter BMD ($P < 0.05$) with improved HRQL ($P < 0.05$) over two years of treatment of once-yearly ZOL 5mg. FI was reduced ($P < 0.05$) with oral daily elemental calcium and vitamin D in the treatment course.

Conclusions: ZOL improves BMD and HRQL, especially in the physical aspects, over two years of treatment in women with postmenopausal osteoporosis, and can help improve balance ability. **(Endokrynol Pol 2014; 65 (2): 96–104)**

Key words: *osteoporosis; zoledronic acid; bone mineral density; quality of life; SF-36; Fall Index (FI)*

Streszczenie

Wstęp: Osteoporoza to schorzenie cechujące się obniżeniem masy kostnej i wytrzymałości mechanicznej kości z towarzyszącym zwiększeniem ryzyka złamań. Złamania osteoporotyczne, będące najpoważniejszym powikłaniem osteoporozy, wiążą się nie tylko z obniżoną gęstością mineralną tkanki kostnej (BMD, *bone mineral density*) ale też z upadkami. Z osteoporozą i złamaniami wiąże się obniżenie jakości życia związanej ze stanem zdrowia (HRQoL, *health-related quality of life*). Kwas zoledronowy (ZOL) to bisfosfonian w postaci dożylnej przeznaczony do podawania raz w roku, w przypadku którego w badaniach klinicznych z grupą kontrolną wykazano skuteczność i bezpieczeństwo w zwiększaniu BMD i zmniejszaniu ryzyka złamań.

Materiał i metody: Autorzy przeprowadzili samodzielnie kontrolowane, prospektywne badanie z udziałem 220 znajdujących się w wieku pomenopauzalnym kobiet z osteoporozą (średnia wieku 67 lat), które otrzymały jednorazowo roztwór ZOL w dawce 5 mg na początku badania i 12 miesięcy później. Na początku badania, w 12. miesiącu i w 24. miesiącu badania (za każdym razem przed podaniem ZOL) oznaczano BMD, HRQoL i wskaźnik upadków (FI, *fall index*). Główne punkty końcowe obejmowały zmiany BMD w odcinku lędźwiowym kręgosłupa i BMD w okolicy biodra, a także zmiany HRQoL w kwestionariuszu SF-36. Dodatkowe porównania będą oparte na FI. W porównaniach wartości BMD, liczby punktów w poszczególnych domenach kwestionariusza SF-36 i wartości FI zastosowano metodę wielokrotnych porównań najmniejszej istotnej różnicy.

Wyniki: U pacjentek stwierdzono znamiennie większe wartości BMD na poziomie L1–4, BMD w całkowitym obszarze biodra, BMD w obrębie szyjki kości udowej oraz BMD w obrębie krętarza ($p < 0,05$) oraz znamienną poprawę HRQoL ($p < 0,05$) w okresie 2 lat leczenia podawanym raz w roku ZOL w dawce 5 mg. Stwierdzono też zmniejszenie FI ($p < 0,05$) dzięki codziennemu przyjmowaniu wapnia i witaminy D w okresie leczenia.

Wnioski: Stosowanie ZOL prowadzi do poprawy BMD i HRQoL, zwłaszcza w aspekcie fizycznym, w okresie 2 lat stosowania u kobiet z osteoporozą pomenopauzalną, i może przyczyniać się do poprawy zdolności utrzymania równowagi. **(Endokrynol Pol 2014; 65 (2): 96–104)**

Słowa kluczowe: *osteoporoza; kwas zoledronowy; gęstość mineralna tkanki kostnej; jakość życia; SF-36; wskaźnik upadków (FI)*

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Introduction

Osteoporosis, a chronic disease that affects an estimated 200 million people worldwide [1], can result in low bone mass and the structural deterioration of bone, ultimately leading to fragility fractures [1, 2]. Postmenopausal women are among those at greatest risk of osteoporosis. Osteoporosis is associated with decreased quality of life [3]. It has been previously shown that postmenopausal and male osteoporotics have poorer health than counterparts with normal BMD, even after adjustment for co-morbidity and prior fracture [4]. Osteoporosis-related fractures are subsequently associated with increased morbidity and mortality, reduced quality of life, and increased use of health care [1].

Decreased bone mass, and associated loss of bone strength, are the main reasons for osteoporosis-related fracture, but another main cause of this kind of fracture is a fall [5–7]. Postural stability and balance decrease with age [8]. Loss of balance and increased body sway are important risk factors for falls in postmenopausal women. The age-associated increase in the incidence of osteoporotic fractures results from a combination of increased fall risk and reduced bone strength. Although various factors are associated with falls, impaired balance and mobility have been consistently identified as the main risk factors [8]. Fall prevention should be routine in the management of postmenopausal women.

The major treatment goal for patients with osteoporosis is to prevent fractures by maintaining or increasing BMD, reducing excessive bone turnover [2] and reducing falls. A number of classes of osteoporosis medication i.e. bisphosphonates (BP), denosumab and selective oestrogen receptor modulators (SORM), have been demonstrated to be effective in reducing the risk of fragility fractures and chronic disability in postmenopausal women [2]. Despite the need for long-term therapy, adherence to osteoporosis medications is not optimal. Roughly three quarters of the women who initiate pharmacological therapy for osteoporosis are no longer adhering to treatment, and approximately 50% have discontinued treatment, after 12 months [9].

Bisphosphonates, a mainstay among the various classes of antiosteoporotic drug, have been shown to increase BMD and to reduce the risk for osteoporotic fractures in numerous clinical trials [4, 10, 11]. Oral bisphosphonates is the first-line treatment for postmenopausal osteoporosis (PMO), but they are poorly absorbed (less than 1%) and may be associated with oesophageal irritation/gastrointestinal (GI) symptoms when used in clinical practice [12–14]. A once-yearly intravenous infusion of zoledronic acid (ZOL) 5mg, the most potent bisphosphonate available, is particularly useful in patients with GI intolerance or GI contraindications to oral bisphosphonates, malabsorption of oral bisphosphonates, and history of poor response to oral therapy [11, 15]. And it has been proved to reduce the risk of vertebral, hip, and other nonvertebral fractures [12, 16, 17]. Idem intervals and 100% bioavailability with *i.v.* bisphosphonate therapy address some of the limitations associated with oral bisphosphonates [15].

The purpose of the present study was to assess the real-life effectiveness of zoledronic acid in the management of patients with postmenopausal osteoporosis over a two year treatment period. We demonstrated the non-inferiority of *i.v.* ZOL 5 mg in increasing BMD and improving HRQL in those patients.

Material and methods

Study design

This was a self-controlled, prospective cohort study of Chinese postmenopausal women being prescribed with ZOL for the management of their osteoporosis. Patients were treated and followed for two years with quarterly telephone interviews and clinic visits at months 12 and 24. Patients received a once-yearly *i.v.* dose of zoledronic acid (Aclasta®; Novartis Pharmaceuticals) at baseline and month 12. Following the baseline visit, during which demographics and baseline parameters were collected, patients were managed as per usual routine care at home. BMD, SF-36 and Fall Index were measured at baseline, month 12 and month 24 (before each use of ZOL). Blood and urine samples were also obtained at baseline, month 12 and month 24 (just before each use of ZOL) for the examination of safety variables. BMD examined by DXA, HRQL assessed by SF-36, and FI derived from balance testing by Sunlight Tetrax balance test system were the outcome measures.

Patients

Postmenopausal women between the ages of 50 and 80 were eligible for inclusion if they had a BMD T-score of −2.5 or less at the femoral neck, total hip or spine (L1–L4) within one month prior to screening, with or without evidence of existing fracture.

Exclusion criteria included:

— active cancer, other metabolic bone disease, secondary causes of osteoporosis;
— prior therapy with bisphosphonates, parathyroid hormone, strontium ranelate, raloxifene, calcitonin, high-dose corticosteroids or hormone replacement within six months prior to baseline;
— concomitant illness that would substantially influence their HRQL;
— calculated creatinine clearance less than 30 ml/min, or urine dipstick more than 2+ protein without evidence of contamination or bacteriuria;

— serum calcium greater than 2.75 mmol/L (11.0 mg/dL) or less than 2.00 mmol/L (8.0 mg/dL);
— active cerebrovascular disease, obvious tremor symptoms, severe visual impairment, severe muscle and nerve lesions, bone and joint deformities, and other states affecting static standing alone.

All subjects received oral daily elemental calcium (1,000 to 1,500 mg) and vitamin D (800 to 1,200 IU). Those who met the study criteria were informed of the nature of the study, and each subject's written informed consent was obtained.

Outcome measures

BMD (bone mineral density)

Dual energy X-ray absorptiometry (DXA) scans of the lumbar spine (L1–L4) and the left hip were performed at baseline and months 12 and 24 using GE-Lunar (iDXA, GE, USA). Besides the total hip, BMD of the femoral neck and trochanter were also measured. The primary outcome measure of the study was the percent change in BMD before and after the use of ZOL.

HRQL: SF-36

HRQL (health-related quality of life) was assessed using the SF-36 questionnaire at baseline and months 12 and 24. This questionnaire assesses eight domains: PF (physical function), RP (role-physical), BP (bodily pain), GH (general health), VT (vitality), SF (social function), RE (role-emotional), MH (mental health), and two summary scores: PCS (physical component summary) and MCS (mental component summary) [18]. PCS is the average of the first four domains, and MCS is the average of the last four domains. Each domain is scored and interpreted separately, rather than obtaining a total score, so each question was analysed individually and grouped according to the domains that they represent. All domain scores range from 0 to 100, with higher scores indicating better HRQL [18].

FI (Fall Index)

Fall Index (FI) was measured by the tetra-ataxiometric posturography system Tetrax® (Sunlight Medical Ltd., Ramat Gan, Israel). Tetrax balance diagnosis is based on the measurement of vertical pressure fluctuations, which is measured in the four independent power boards. The four measuring points represent forefeet and heels of two feet respectively. Some studies [19–21] conducted with this method have demonstrated the predictive ability of the risk of falls. There are a total of eight postures, each posture for about 32 seconds. Eight static postures include:

— NO (Standing on a fixed metal platform with No pads, head straight with eye Open),
— NC (Standing on a fixed metal platform with No pads, head straight with eye Closed),
— PO (Standing on elastic Pads with eyes Open),
— PC (Standing on elastic Pads with eyes Closed),
— HR (Keep eyes closed and standing on elastic pads, turn Head to the Right),
— HL (Keep eyes closed and standing on elastic pads, turn Head to the Left),
— HB (Keep eyes closed and standing on elastic pads, Head Back up 30 degrees),
— HF (Keep eyes closed and standing on elastic pads, Head Forward down 30 degrees). The postural control parameters provide valuable diagnostic information and fall risk calculation. It is based on the patient's body shaking frequency and amplitude, as well as movement of the centre of gravity to assess the patient's balance control ability, and then integrating the balance indicators to predict the risk of falls. Fall Index reflects the risk of falls, ranging from 0 to 100, with a higher FI indicating a higher fall risk. FI is divided into three levels: 0–36 meaning low risk of falls, 36–58 meaning medium risk, and 58-100 meaning high risk.

Safety variables

All AEs and serious AEs (SAEs) were recorded for safety assessment. This also included physical examination, regular measurement of vital signs, haematology, blood chemistry, urinalysis, assessments of renal abnormalities (pre- and postdose administration), postdose symptoms (fever, headache, myalgia, arthralgia), and cardiovascular and gastrointestinal events.

Statistical analysis

Data was entered into the Microsoft Office Excel 2007 program. Statistical analyses were performed using SPSS for Windows (version 17.0). Data was presented by descriptive analysis with means ± standard deviations. The percentage change in BMD and FI was defined as (1-year score–baseline score) / (baseline score) × 100%. ANOVA and LSD multiple comparison was used for statistical comparison of BMD, SF-36 domain scores and FI. A P-value of < 0.05 was required for statistical significance.

Results

Patients and characteristics

A total of 246 patients diagnosed with osteoporosis agreed to participate in the study; 26 were excluded by the exclusion criteria. Baseline characteristics are shown in Table I. Of the 220 women at baseline, 213 (97.7%) came back for review one year later, and 203 (92.3%) finished the total two-year follow-up. The return rate of patients was high, with some expected shedding during the study as a consequence of the length of follow-up.

Table I. *Basic characteristics of 220 postmenopausal osteoporotic patients*

Tabela I. *Charakterystyka wyjściowa 220 kobiet z osteoporozą pomenopauzalną*

Variable	Mean ± SD
Age (years)	67.21 ± 9.11
Height [cm]	154.75 ± 6.04
Weight [kg]	55.99 ± 10.38
BMI [kg/m^2]	23.38 ± 3.40
Menopausal age (years)	48.00 ± 3.89

Outcome evaluation of bone (BMD)

The mean BMD was measured every time and the mean percentage changes in BMD from baseline at lumbar spine (L1-4), total hip, femoral neck and trochanter are shown in Table II and Figure 1. By ANOVA and LSD multiple comparison, BMD increased significantly at lumbar spine (3.93%), total hip (2.81%), femoral neck (2.69%), and trochanter (3.95%) at month 12 compared to baseline ($P < 0.05$ for all comparisons). Statistically significant increases ($P < 0.05$) were also seen at month 24 at all sites examined. The percentage increases in lumbar spine, total hip, femoral neck, and trochanter were 5.71%, 3.72%, 3.36%, 4.57%, respectively.

Outcome evaluation of HRQL (SF-36)

Table III shows details of the response changes to the SF-36 questionnaire after 12 and 24 months of treatment. Improvement after the first treatment course (12 months) was significant in the following domains: bodily pain, general health and social function ($p < 0.05$). There was a significant improvement in the following domains of SF-36 after 24 months of treatment compared to baseline: bodily pain, general health and vitality ($p < 0.05$). In addition, the once-yearly ZOL 5 mg increased SF-36 physical component summary (PCS) score significantly ($P < 0.001$) each year. However, changes in emotional component summary (MCS) score between the baseline and months 12 or 24 did not reach statistical significance, although some rising trends were observed. Figure 2 shows the scores for the eight domains of SF-36 before and after treatment.

Outcome evaluation of balance (FI)

As another outcome, Fall Index decreased significantly ($P < 0.001$) during the first treatment course (12 months) and kept decreasing at month 24 ($P < 0.001$). The percentage decrease was 28.0% and 48.0% at month 12 and month 24 respectively, compared to baseline (Table II and Figure 1).

Adverse events

Adverse events (AEs) were assessed, and physical examinations and laboratory tests were obtained for safety evaluation. Eight patients experienced AEs that led to a discontinuation of the study. No subject died during the study period.

The most common AEs observed with ZOL are acute-phase reactions (APRs). The APRs happening in our study were flu-like symptoms (8.1%), fever (17.9%), headache (6.7%), myalgia/arthralgia (12.5%), and nausea/vomiting (5.6%) (Table 4).

No hypocalcaemia, inflammatory ocular disorders, osteonecrosis of the jaw, or atrial fibrillation (AF) was observed. No significant abnormalities in the defined haematology or biochemistry parameters were found in this study. Ten (4.6%) patients had renal events, five of which had small and transient increases in serum creatinine level, and in the other five patients urinary protein > 2+ appeared. Five (2.1%) patients had cardiovascular events, four of which were diagnosed as coronary heart disease, and the other one (0.4%) as atrioventricular block. The incidence rate of clinical fracture in 24 months was 7.6%.

Table II. *Changes in bone mineral density and Fall Index after 12 months and 24 months of treatment with zoledronic acid in postmenopausal osteoporotic patients*

Tabela II. *Zmiany gęstości mineralnej tkanki kostnej i wskaźnika upadków po 12 miesiącach i po 24 miesiącach leczenia kwasem zoledronowym u kobiet z osteoporozą pomenopauzalną*

Bone mineral density (g/cm^2)	Baseline (a) (n = 220)	12 month (b) (n = 215)	24 month (c) (n = 203)	% change (a–b)	% change (a–c)	Significance (P-value)# (a–b)	Significance (P-value)# (a–c)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
Lumbar spine (L1-4)	0.793 ± 0.137	0.822 ± 0.143	0.841 ± 0.134	3.93 ± 0.34	5.71 ± 0.35	< 0.05	< 0.001
Total hip	0.702 ± 0.103	0.723 ± 0.112	0.730 ± 0.096	2.81 ± 0.32	3.72 ± 0.46	< 0.05	< 0.01
Femoral neck	0.670 ± 0.104	0.690 ± 0.086	0.695 ± 0.073	2.69 ± 0.46	3.36 ± 0.60	< 0.05	< 0.01
Trochanter	0.533 ± 0.098	0.553 ± 0.136	0.559 ± 0.056	3.95 ± 0.61	4.57 ± 0.73	< 0.05	< 0.05
Fall Index (FI)	52.95 ± 10.94	38.23 ± 15.51	27.02 ± 12.81	28.0 ± 12.8	48.0 ± 9.3	< 0.001	< 0.001

P-value is derived by LSD multiple comparison among BMDs of Baseline, 12 month and 24 month

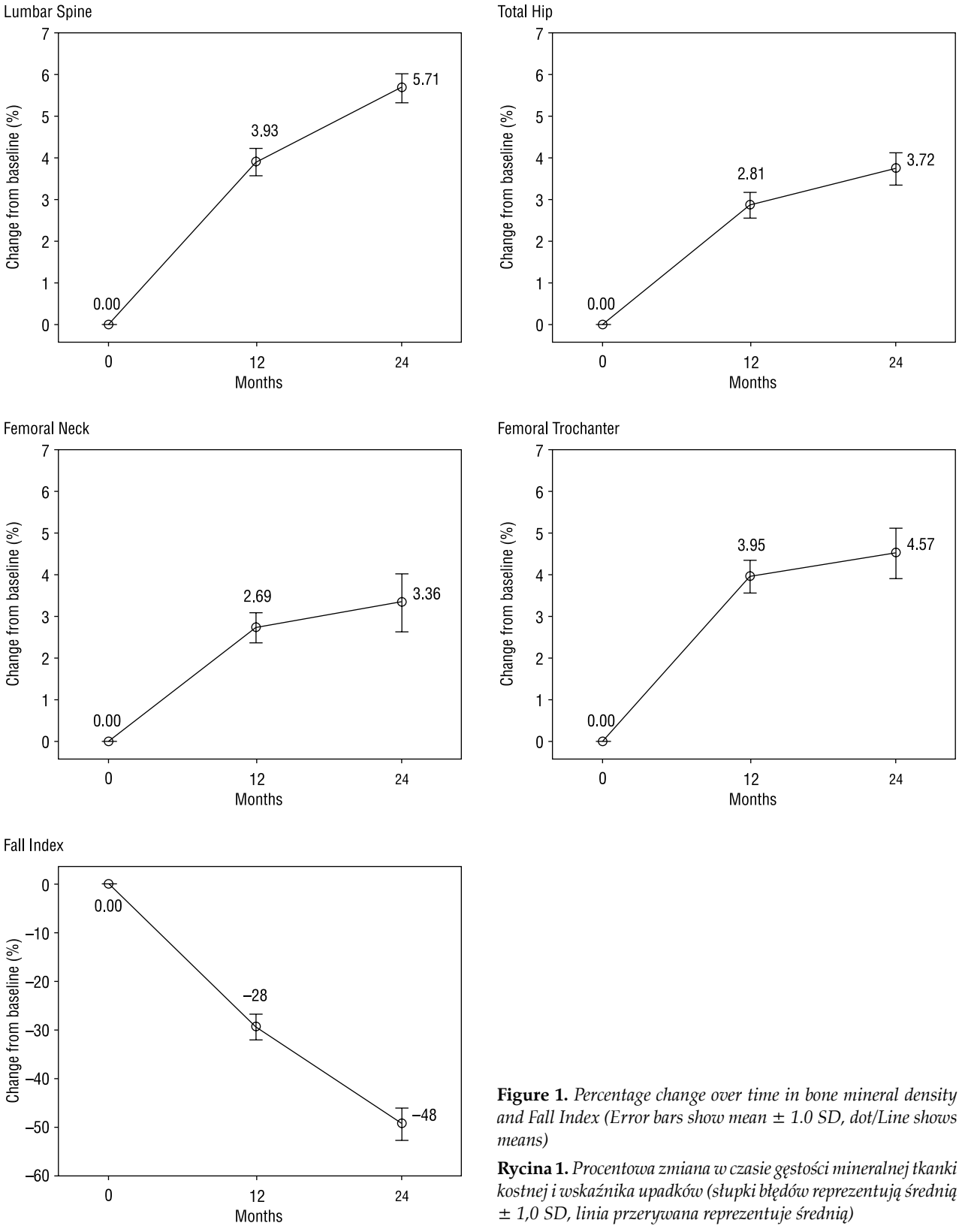

Figure 1. *Percentage change over time in bone mineral density and Fall Index (Error bars show mean ± 1.0 SD, dot/Line shows means)*

Rycina 1. *Procentowa zmiana w czasie gęstości mineralnej tkanki kostnej i wskaźnika upadków (słupki błędów reprezentują średnią ± 1,0 SD, linia przerywana reprezentuje średnią)*

Discussion

Currently, the endpoint in the treatment of osteoporosis is considered to be the prevention of fracture, with an increase of BMD as a surrogate endpoint. A lot of studies have confirmed the benefit of once-yearly ZOL 5 mg. They have demonstrated that ZOL significantly reduces the risk of morphometric vertebral fracture and clinical vertebral fracture, and increases total hip, femoral neck, and trochanter BMD [12, 15, 22, 23]. A few studies have

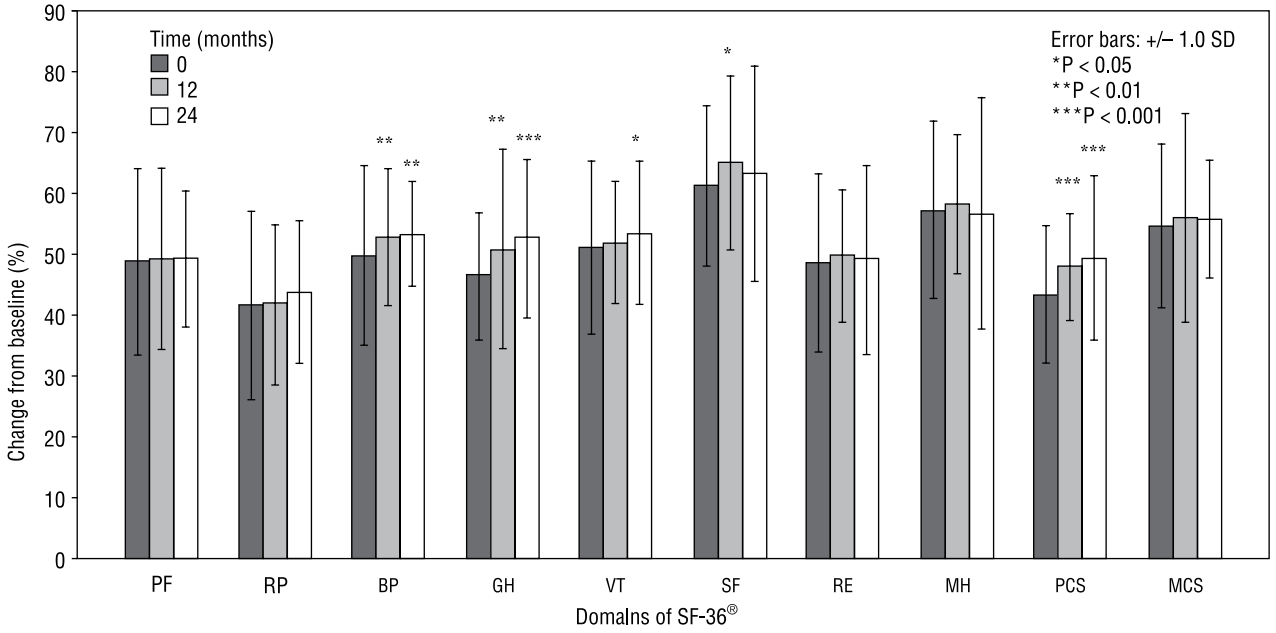

Figure 2. *Mean scores of domains (SF-36®) at different times*

Rycina 2. *Średnie liczby punktów w poszczególnych domenach kwestionariusza SF-36® w poszczególnych punktach czasowych P-value is from Table III. PF — physical function; RP — role-physical; BP — bodily pain; GH — general health; VT — vitality; SF — social function; RE — role-emotional; MH — mental health; PCS — physical component summary; MCS — mental component summary*

Table III. ***Changes in domains of SF-36 after 12 months and 24 months of treatment with zoledronic acid in postmenopausal osteoporotic patients***

Tabela III. ***Zmiany liczby punktów w poszczególnych domenach kwestionariusza SF-36 po 12 miesiącach i po 24 miesiącach leczenia kwasem zoledronowym u kobiet z osteoporozą pomenopauzalną***

SF-36	Baseline (a) (n = 220)	12month (b) (n = 215)	24month (c) (n = 203)	Significance (P-value)#	
	Mean ± SD	Mean ± SD	Mean ± SD	(a–b)	(a–c)
PF	48.7 ± 15.1	49.2 ± 14.9	49.1 ± 11.0	> 0.05	> 0.05
RP	41.4 ± 15.5	41.7 ± 13.0	43.6 ± 11.8	> 0.05	> 0.05
BP	49.7 ± 14.7	52.6 ± 11.2	53.2 ± 8.7	< 0.01	< 0.01
GH	46.3 ± 10.3	50.7 ± 16.3	52.5 ± 12.9	< 0.01	< 0.001
VT	50.9 ± 14.2	51.8 ± 9.9	53.4 ± 11.6	> 0.05	< 0.05
SF	60.9 ± 13.2	64.9 ± 14.1	63.1 ± 17.8	< 0.05	> 0.05
RE	48.4 ± 14.7	49.5 ± 10.8	49.0 ± 15.5	> 0.05	> 0.05
MH	57.1 ± 14.5	58.1 ± 11.4	56.6 ± 18.9	> 0.05	> 0.05
PCS	43.4 ± 11.2	47.9 ± 8.7	49.1 ± 13.5	< 0.001	< 0.001
MCS	54.5 ± 13.3	55.9 ± 17.0	55.5 ± 9.7	> 0.05	> 0.05

P-value is derived by LSD multiple comparison among the scores of Baseline, 12 month and 24 month

Table IV. *Adverse Events and clinical fracture*

Tabela IV. *Zdarzenia niepożądane i złamania kliniczne*

AEs	N (%)	Study-related
Flu-like symptoms	18 (8.1%)	Yes
Fever	39 (17.9%)	Yes
Headache	15 (6.7%)	Yes
Myalgia/arthralgia	27 (12.5%)	Yes
Nausea/vomiting	12 (5.6%)	Possibly
Renal events	10 (4.6%)	Possibly
Cardiovascular events	5 (2.1%)	Possibly
Clinical fracture	17 (7.6%)	–

AEs not related to the study are not listed above

pointed out that the increasing effect of ZOL on bone mineral density would continue with the increasing time of injections [22, 24]. So we supposed that over a two-year period, use of once-yearly ZOL 5 mg, BMD would continue to show improvements.

The results showed that statistically significant increases ($P < 0.05$) were seen at months 12 and 24 at all sites examined, and the increase percentage at month 24 was higher than month 12. The results of our study are consistent with the previous reported ones.

Many studies have noted that osteoporotic patients have impaired HRQL, especially in the physical aspects, and fracture is an important determinant of HRQL impairment in these patients [25–27]. One study showed that lower femoral neck BMD was associated with poorer PF [3]. Although the increase of BMD is very important in the treatment of osteoporosis, the measurement of HRQL is indispensable for the evaluation of osteoporotic patients, and the improvement

of HRQL is an important additional endpoint to consider the efficacy of osteoporosis treatment. It should be noted that treatment of low BMD in osteoporotic individuals is known to be associated with improved quality of life [27].

However, there is little data directly assessing the effects of bisphosphonate treatment on HRQL in postmenopausal women with osteoporosis. In an analysis of the HORIZON-PFT trial, patients treated with ZOL experienced significantly fewer days of limited activity caused by back pain or fracture compared to those receiving a placebo [28]. And it has been reported that ZOL therapy also reduces the number of bed days due to a fracture [29]. In our study, the hypotheses were that over a two-year period of use of once-yearly ZOL 5 mg, HRQL would be maintained or improved owing to a higher BMD and better balance. This was indeed confirmed in our analysis of the data. After the first treatment course (12 months), BP, GH and SF were significantly improved. And after 24 months of treatment, BP, GH and VT were significantly improved. BP is clinically important in osteoporosis, as it frequently appears as the first symptom of established osteoporosis. So the improvement of BP is particularly important in the treatment of osteoporosis patients. In our study, PCS was significantly increased over two years of treatment ($P < 0.001$ each year). This provides support for the effect of ZOL on the physical well-being of the patient. With HRQL declining with age, although MCS was only very slightly increased (not significantly) in our study, an improvement or maintenance in MCS still suggests that negative feelings are reduced in patients treated with ZOL.

The risk of osteoporotic fracture is mainly determined by BMD. But its relationship with falls is also very close. Some studies have even pointed out that falls may have a more important role in fracture risk [30], especially in vertebral fracture and hip fracture. Falls are multifactorial, and their intrinsic causes include altered balance, gait, muscle strength, visual acuity, cognition, and the presence of chronic diseases [31]. Almost all hip fractures (more than 90%) occur as the result of a fall. These fractures are related not only to the decreased bone mass, but also to other factors such as reduction of balance and of muscle strength and power in the lower extremities [31]. However, few studies have taken into consideration the relationship between treatment of ZOL and risk of falls. In this study, we used the tetra-ataxiometric posturography system Tetrax® to evaluate the balance ability, and then predict the fall risk [19–21]. The lower FI will lead to the lower risk of falls, with less fracture being caused subsequently [19]. The results showed that over two years of annual treatment of zoledronic acid, the risk of falls was reduced.

On the one hand, Silva [32] reported that the risk for falls in women with osteoporosis was twofold higher than those with normal bone mass. As mentioned above, ZOL increases BMD, and thus it could reduce the risk of falls to a certain extent. On the other hand, it is known that osteoporosis can lead to spinal deformities such as thoracic kyphosis due to vertebral compression that alters the structure of the spine, causing weakness of the extensor muscles of the trunk and leading to reduced physical mobility and flexibility [33]. When ZOL increases BMD and improves the bone status, the extensor muscles of the trunk are also improved. Once the patients have a good posture and become more stable, the risk of falls is naturally reduced. In addition, all the patients received daily calcium (1,000–1,500 mg) and vitamin D (400–1,200 IU) during the study. Muscle strength, balance, and functional mobility depend on vitamin D serum levels [34, 35]. Several previous studies have noted that treatment with vitamin D (alfacalcidol or calcitriol) can significantly reduce the risk of falls and of fall-associated fractures [34, 36, 37]. Hua Lin [23, 38] reported that 5 mg zoledronic acid and calcitriol can significantly reduce the risk of falls in patients with postmenopausal osteoporosis. Therefore, vitamin D used in our study also had played an important role via its influence on muscle, bone and neuromuscular transmission or cognition.

Studies with ZOL have generally shown it to be safe and well tolerated with no clear indication of drug-related serious adverse events except the story of AF in the HORIZON PFT [39]. Usually AEs after using once-yearly ZOL 5 mg were clustered into five groups: acute-phase reactions, such as fever, musculoskeletal, gastrointestinal; hypocalcaemia; renal dysfunction; cardiovascular; eye inflammation; and osteonecrosis of the jaw [40–42].

The most common AEs observed with ZOL are acute-phase reactions (APRs) [43], usually characterised by flu-like symptoms, headache, fever, arthralgia, and myalgia. Most of these symptoms occur within the first three days after infusion and tend to be resolved within several days after administration. The risk of an APR may be reduced by the administration of a nonsteroidal anti-inflammatory drug or acetaminophen prior to injection and over the following three days [44]. APRs have been reported in patients on oral as well as *i.v.* bisphosphonates, and appear to be caused, at least in part, by the release of inflammatory cytokines from circulating T cells. In our study, most APRs were easily managed with a nonsteroidal anti-inflammatory drug or acetaminophen. With the supplement of oral daily elemental calcium (1,000 to 1,500 mg) and vitamin D (800 to 1,200 IU), no one ever had hypocalcaemia during the study. Evaluation of the renal safety of ZOL in

several studies has shown that administration of ZOL was not associated with any long-term detrimental effects on renal function [45]. Generally, the renal effects were short term, mild, and transient. In our study, only small and transient increases in serum creatinine levels and urinary protein were observed. Over two years, there was neither systematic change in serum creatinine nor deterioration in calculated creatinine clearance. No study has established biological mechanisms that might link bisphosphonate therapy to atrial fibrillation or arrhythmia. An increased risk of serious atrial fibrillation has not been previously associated with zoledronic acid or other bisphosphonates [46], although a letter in this issue reports a similar, though nonsignificant, trend from the 1997 Fracture Intervention Trial of alendronate [47]. And in the HORIZON-PFT, an increased incidence of serious AF which were uniformly distributed over time was observed in the zoledronic acid group compared to the placebo group [39]. However, larger epidemiological studies have found no increased risk of AF in patients receiving bisphosphonate treatment. No atrial fibrillation was observed in this study. There was a small increase in the risk of inflammatory ocular adverse events within the first 15 days after ZOL infusion, as reported previously [39]. In HORIZON-RFT, only one case of iritis was reported in the ZOL group [48]. All such events were treated and resolved with outpatient treatment. However, no spontaneous report of eye inflammation was observed in this study. Most cases of osteonecrosis of the jaw have been observed in patients with cancer who were treated with frequent doses of intravenous bisphosphonates [12, 49]. In addition, many studies suggest that, to women with postmenopausal osteoporosis, a once-yearly regimen with intravenous zoledronic acid does not appear to affect the frequency of osteonecrosis of the jaw [12], as our study showed.

So we concluded that ZOL 5 mg treatment was generally safe and well tolerated.

Several limitations to this study design should be noted. The first is the small number of subjects and the short study duration. Secondly, as noted earlier in the text, a control group (placebo) was not included because it was thought to be unethical to deny active treatment to patients with osteoporosis. Thirdly, biochemical bone turnover markers were not measured like other studies. Furthermore, we didn't try to find the relationships among the changes of BMD, FI and SF-36 score, and further studies are required. Finally, as many studies show, previous fractures have an impact on HRQL, and HRQL will decrease with each subsequent fracture [25, 26]. Some patients in our study had previous fractures, but we didn't have these patients divided into two groups (fracture or no). Further studies are required in which patients would be divided into a fracture group and a non-fracture group to see the treatment outcome respectively. However, it is important to note that in this clinical trial, 92.3% of patients received both of two infusions over two years, demonstrating a very high compliance with therapy.

Conclusions

A once-yearly infusion of zoledronic acid during a two-year period was associated with a significant and sustained increase in the BMD (lumbar spine, total hip, femoral neck, and trochanter) and an improvement in HRQL, especially in the physical aspects. And with the supplement of oral daily elemental calcium and vitamin D, a better balance ability was obtained after the treatment course. In addition, the treatment had a favourable safety profile and was generally well tolerated.

Given the relatively poor adherence to oral bisphosphonate therapy in clinical practice, an annual infusion of zoledronic acid may provide a promising approach to treating osteoporosis and reducing the risk of osteoporotic fracture.

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