

The effect of risedronate (17.5 mg/week) treatment on quality of life in Japanese women with osteoporosis: a prospective observational study

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Abstract A prospective observational study to test the effects of risedronate 17.5 mg/week treatment on quality of life (QOL) of 1,363 Japanese female patients with osteoporosis showed QOL improvement after 12 weeks of administration. Comorbid factors such as ischemic heart disease, hip osteoarthritis, and higher values of FRAX blunted the effects of QOL of the treatment. Few studies have investigated the effect of osteoporosis treatment on QOL in relationship to comorbid factors other than osteoporosis and fracture. Efficacy was determined by changes over time in EQ-5D at baseline, at 12 and 24 weeks, and at the final assessment. Factors affecting changes in EQ-5D were evaluated with a multivariate analysis. Safety was determined by assessing the incident rate of adverse events. The improvement of EQ-5D compared to baseline was observed as significant after 12 weeks of treatment ($p < 0.001$). The greatest

improvement was observed in the dimension of “pain/discomfort” by the multivariate analysis ($p < 0.001$). Factors affecting QOL improvement were FRAX value without BMD, age, glucocorticoid use, ischemic heart disease, hip osteoarthritis, and pain. The incidence rate of drug-related adverse events was 4.72 % (95 % confidence interval 3.63–6.02 %). Risedronate at 17.5 mg/week improved the QOL in patients with osteoporosis among Japanese women, and comorbidity factors decreased the effects.

Keywords EQ-5D · FRAX · Comorbid factors · Ischemic heart disease · Osteoarthritis

Introduction

Osteoporosis is a skeletal disease with an increased risk of fractures [1]. Commonly associated diseases relating to lifestyle have been shown to increase the risk of fractures, consequently affecting the quality of life (QOL) of patients with osteoporosis. These diseases include ischemic heart disease [2], hypertension [2, 3], heart failure [2–4], diabetes [5–7], arteriosclerosis [2, 8, 9], and dyslipidemia [9–11]. Joint diseases including rheumatoid arthritis [12–14] and hip and knee osteoarthritis are also shown to reduce QOL [15–19]. However, the effect of comorbid factors in patients with osteoporosis has not been well investigated in relationship to the efficacy of improvement in QOL by treatment of osteoporosis. In this prospective observational study, we investigated the effects of risedronate (Actonel tablet) 17.5 mg/week on QOL improvement and safety in patients with osteoporosis. We also analyzed the effects of comorbid factors on QOL using EQ-5D [20, 21].

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Materials and methods

Study design and subjects

The present study was conducted in 307 medical institutions in Japan. The registration period was from November 2008 through June 2009: 1,363 women with osteoporosis who had not previously been treated with risedronate (17.5 mg/week) were registered prospectively by the central registration method, and the study period was set to continue until June 2010. Eligible subjects were those given diagnosis of osteoporosis using the criteria of the Japanese Primary Osteoporosis Diagnosis (2000 revised version) who had a QOL evaluation at baseline using the Japanese version of the EQ-5D at baseline. The study period was 24 weeks from the start of risedronate weekly administration with evaluations performed at 12 and 24 weeks. The data at 12 or 24 weeks were used for the final assessment depending on the follow-up period of the patients. Items for assessment included age, gender, height, weight, and prevalent comorbid factors. The primary efficacy endpoint was the utility value of the EQ-5D. Adverse events (AEs) were also examined by type and degree of severity.

The present study was conducted in compliance with ministerial ordinances concerning investigation after manufacturing and sales of Japanese medicines and study performance criteria GPSP (Good Post-marketing Study Practice).

EQ-5D

The EQ-5D consists of five dimensions (5D) and a visual assessment scale (VAS) [20, 21]. The five dimensions are “mobility,” “self-care,” “usual activities,” “pain/discomfort,” and “anxiety/depression”; each dimension was evaluated by three levels of grading. Subsequently, the scores obtained from the subjects were converted to utility values (EQ-5D[utility]) (−0.111 to 1.000) using the HRQOL score conversion table. For the VAS assessment, subjects evaluated their health status ranging from “best imaginable health state” (100) to “worst imaginable health state” (0). Background factors influencing changes in EQ-5D[utility] at the final assessment were investigated. When one or more levels of the grading increased from baseline in each dimension, the value of 1 was assigned for “Improved,” and when one or more level decreased or did not change, the value of 0 was assigned for “Not improved.”

FRAX (fracture risk assessment tool)

At registration, the values of major osteoporotic fracture risk and hip fracture risk without bone mineral density (FRAX without BMD) were calculated by entering risk

factors into the Japanese version of the Fracture Risk Assessment Tool (FRAX[®]) (Web Version 3.1). The entered risk factors were age, gender, height, weight, previous fracture, parent had fractured hip, current smoking, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, and alcohol intake (3 or more units/day). When required items were entered as “Unknown” [except for age, gender, and body mass index (BMI)], they were described as “None.”

Statistical analysis

To identify differences in the value of EQ-5D[utility] between two time points, a paired *t* test was used (Fig. 1). In addition, a two-sample *t* test was also performed to compare two level factors. An analysis of variance (ANOVA) was done to compare three or more level factors. For efficacy analyses, differences in the values of EQ-5D[utility] between baseline and the final assessment were used for the five dimensions as criterion variables, using multivariate analyses (Table 2). To investigate the comorbid factors influencing EQ-5D[utility] changes, multiple variable analyses were also performed (Table 3). For safety analyses, the incidence rates of AEs were calculated by preferred term (PT) (Table 4). All statistical analyses were performed SAS (ver. 8.2 or later). A two-sided 95 % confidence interval (95 % CI) was used for estimation of interval. A value of $p < 0.05$ was considered statistically significant.

Results

Subjects

During the registration period, 1,363 subjects were enrolled. Questionnaires were collected from 1,356 subjects, and

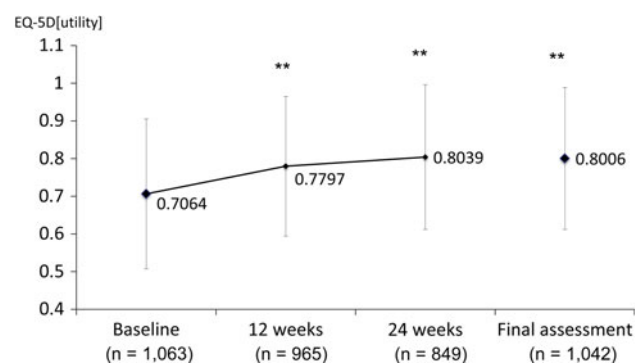


Fig. 1 Change over time in EQ-5D[utility]. Data represented are mean \pm SD. ** $p < 0.001$ versus baseline (by paired *t* test). The mean EQ-5D[utility] changes from baseline were 0.0724 ± 0.1648 , 0.0945 ± 0.1777 , and 0.0933 ± 0.1762 at 12 weeks, 24 weeks, and the final assessment, respectively

for 1,069 subjects whose EQ-5, BMD, or bone metabolism markers were evaluated at baseline the efficacy analysis was performed. The safety analysis included 1,292 subjects; the 223 subjects who were not evaluated for reason of missing data at the final assessment were excluded from the safety analysis.

The discontinuation rate was 9.45 % (101 of 1,069 subjects). No significant differences were detected in EQ-5D[utility] values between subjects who discontinued or completed the study at the baseline, 12 weeks, 24 weeks, or at the final assessment ($p = 0.644, 0.911, 0.388, \text{ and } 0.340$, respectively; two-sample t test). The reasons for discontinuation were “not visit again (70 cases),” “adverse events (14 cases),” “refusal to the treatment (7 cases),” “invalid (4 cases),” and others (9 cases) (duplicate tabulation).

Baseline characteristics of the subject

The baseline characteristics of the 1,069 subjects included in the efficacy analysis are shown in Table 1. The mean age (\pm SD) was 73.5 ± 8.9 years. The mean duration of osteoporosis after the period of diagnosis was 1.94 ± 3.98 years. The mean values of EQ-5D[utility] and EQ-5D[VAS] were 0.7064 ± 0.1991 and 63.70 ± 19.25 . The mean FRAX without BMD and FRAX Hip without BMD were 19.05 ± 10.71 and 7.78 ± 7.35 , respectively.

Efficacy assessment

The mean values of the EQ-5D[utility] were 0.7064 ± 0.1991 (baseline), 0.7797 ± 0.1855 (12 weeks), 0.8039 ± 0.1921 (24 weeks), and 0.8006 ± 0.1885 (final) (Fig. 1). The differences from baseline were significant ($p < 0.001$) starting at 12 weeks. The mean values and the changes in EQ-5D[VAS] were also increased. The estimated values of each explanatory variable by multivariate analysis at the final assessment were 0.195 ($p < 0.001$) for pain/discomfort, 0.134 ($p < 0.001$) for mobility, 0.078 ($p < 0.001$) for anxiety/depression, 0.064 ($p < 0.001$) for usual activities, and 0.051 ($p < 0.001$) for self-care (Table 2).

Pain showed a significant increase at the final assessment with an estimated value of 0.123 ($p = 0.028$) (Table 3). Factors that contributed to reduce the EQ-5D[utility] values during the treatment were age (estimated value $-0.003, p < 0.001$), glucocorticoid use (estimated value $-0.056, p = 0.041$), ischemic heart disease (estimated value $-0.059, p = 0.045$), and hip osteoarthritis (estimated value $-0.130, p = 0.013$). Factors that did not affect the EQ-5D[utility] were BMI, previous fracture, parent fractured hip, current smoking, rheumatoid arthritis, secondary osteoporosis, alcohol intake (3 or more units/day), arrhythmia, heart failure, hypertension, arteriosclerosis,

Table 1 Characteristics of patients (efficacy analysis set)

Number of subjects (<i>n</i>)	1,069
Age, mean \pm SD (years)	73.5 \pm 8.9
Height, mean \pm SD (cm)	149.28 \pm 6.50
Weight, mean \pm SD (kg)	49.68 \pm 7.87
BMI, mean \pm SD (kg/m ²)	22.32 \pm 3.26
Duration of osteoporosis, mean \pm SD (years)	1.94 \pm 3.98
EQ-5D utility, mean \pm SD	0.7064 \pm 0.1991
EQ-5D VAS, mean \pm SD	63.70 \pm 19.25
FRAX without BMD, mean \pm SD	19.05 \pm 10.71
FRAX Hip without BMD, mean \pm SD	7.78 \pm 7.35
Previous fractures (%)	27.69
Pretreatment for osteoporosis	
None (%)	93.36
Switch from other bisphosphonate (%)	6.64
Complications	
Present (%)	81.57
Hypertension (%)	33.30
Dyslipidemia (%)	14.97
Diabetes (%)	7.20
Knee osteoarthritis (%)	10.76

SD standard deviation, BMI body mass index, BMD bone mineral density, FRAX major osteoporotic fracture risk, FRAX Hip hip fracture risk

Table 2 Five dimensions influencing EQ-5D utility changes at the final assessment

Explanatory variable	Multivariate model (<i>n</i> = 1,037)		
	Estimate	95 % (CI)	<i>p</i> value
Improvement of mobility (no: 0, yes: 1)	0.134	0.117 to 0.150	<0.001*
Improvement of self-care (no: 0, yes: 1)	0.051	0.035 to 0.068	<0.001*
Improvement of usual activities (no: 0, yes: 1)	0.064	0.048 to 0.080	<0.001*
Improvement of pain/discomfort (no: 0, yes: 1)	0.195	0.182 to 0.207	<0.001*
Improvement of anxiety/depression (no: 0, yes: 1)	0.078	0.063 to 0.093	<0.001*

CI confidence interval

* $p < 0.05$

diabetes, dyslipidemia, cervical spondylosis, lumbar spondylosis, knee osteoarthritis, spinal canal stenosis, and concomitant use of NSAIDs.

In a multivariate analysis model where the fracture risk factor is replaced with FRAX without BMD as an explanatory variable, factors that decreased EQ-5D[utility] were the FRAX without BMD value (estimated value $-0.002, p < 0.001$) and hip osteoarthritis (estimated value $-0.125, p = 0.017$). The changes in EQ-5D[utility]

Table 3 Factors influencing EQ-5D utility changes at the final assessment

Explanatory variable	Multivariate model (<i>n</i> = 750)		
	Estimate	95 % (CI)	<i>p</i> value
EQ-5D utility at baseline	−0.500	−0.558 to −0.441	<0.001*
Age	−0.003	−0.005 to −0.002	<0.001*
Body mass index (BMI)	−0.003	−0.006 to −0.001	0.132
Previous fracture (no: 0, yes: 1)	−0.011	−0.036 to 0.014	0.377
Parent fractured hip (no: 0, yes: 1)	−0.043	−0.116 to 0.030	0.251
Current smoking (no: 0, yes: 1)	−0.037	−0.116 to 0.042	0.357
Glucocorticoid use (no: 0, yes: 1)	−0.056	−0.111 to −0.002	0.041*
Rheumatoid arthritis (no: 0, yes: 1)	−0.027	−0.081 to 0.027	0.334
Secondary osteoporosis (no: 0, yes: 1)	−0.004	−0.060 to 0.053	0.896
Alcohol intake ^a (no: 0, yes: 1)	0.069	−0.077 to 0.215	0.350
Ischemic heart disease (no: 0, yes: 1)	−0.059	−0.117 to −0.001	0.045*
Arrhythmia (no: 0, yes: 1)	−0.025	−0.096 to 0.045	0.478
Heart failure (no: 0, yes: 1)	−0.015	−0.101 to 0.072	0.736
Hypertension (no: 0, yes: 1)	0.001	−0.023 to 0.026	0.920
Arteriosclerosis (no: 0, yes: 1)	0.035	−0.041 to 0.111	0.365
Diabetes (no: 0, yes: 1)	0.001	−0.039 to 0.042	0.943
Dyslipidemia (no: 0, yes: 1)	0.004	−0.025 to 0.033	0.786
Cervical spondylosis (no: 0, yes: 1)	−0.051	−0.200 to 0.098	0.501
Lumbar spondylosis (no: 0, yes: 1)	0.046	−0.052 to 0.145	0.358
Hip osteoarthritis (no: 0, yes: 1)	−0.130	−0.232 to −0.027	0.013*
Knee osteoarthritis (no: 0, yes: 1)	0.023	−0.013 to 0.059	0.207
Spinal canal stenosis (no: 0, yes: 1)	−0.022	−0.067 to 0.024	0.344
Pain (no: 0, yes: 1)	0.123	0.013 to 0.232	0.028*
NSAIDs ^b (no: 0, yes: 1)	−0.018	−0.042 to 0.006	0.134

^a More than 3 units/day^b Including external preparation* *p* < 0.05**Table 4** Summary of adverse events (safety analysis set)

Number of patients	1,292
Adverse events ^a	112 (8.67 %), (95 % CI 7.19 to 10.34 %)
Drug-related adverse events ^a	61 (4.72 %), (95 % CI 3.63 to 6.02 %)
Abdominal discomfort	14 (1.08 %)
Upper abdominal pain	9 (0.70 %)
Dyspepsia	7 (0.54 %)
Diarrhea	4 (0.31 %)
Gastric ulcer	3 (0.23 %)
Nausea	2 (0.15 %)
Reflux esophagitis ^b	2 (0.15 %)
Malaise	2 (0.15 %)
Dizziness	2 (0.15 %)

^a Patients who experienced one or more adverse events were counted only once^b Unexpected drug-related adverse event from “Precaution for use”

significantly correlated with FRAX values without BMD at baseline (coefficients of correlation −0.29), but the changes in EQ-5D[VAS] did not correlate with the FRAX without BMD baseline values.

Adverse events

In the safety analysis (1,292 subjects), AEs were observed in 112 cases. The incidence rate was 8.672 % with a 95 % CI of 7.19–10.34 %. Drug-related AEs were observed in 61 cases (4.72 %, 95 % CI 3.63–6.02 %). The major drug-related AEs were “abdominal discomfort” (14 cases, 1.08 %), “upper abdominal pain” (9 cases, 0.70 %), “dyspepsia” (7 cases, 0.54 %), “gastritis” (4 cases, 0.31 %), “diarrhea” (3 cases, 0.23 %), and “dizziness,” “gastric ulcer,” “nausea,” “reflux esophagitis,” and “malaise” (2 cases each, 0.15 %) (Table 4). The most frequent drug-related AEs were gastrointestinal disorders (50 cases, 3.56 %). Serious drug-related AEs included “osteomyelitis” and “cholelithiasis,” in 1 case each (0.08 %).

Discussion

The results of the present study demonstrated significant improvement in the QOL values of EQ-5D in patients with osteoporosis after 12 weeks of risedronate treatment. The highest improvement in the criteria of EQ-5D[utility] was

found in the “pain/discomfort” category. We also found that the factors attenuating the effect of risedronate on QOL were age, ischemic heart disease, hip osteoarthritis, and glucocorticoid use. The FRAX values without BMD affected the efficacy of the treatment on the QOL.

Improvement of pain with the treatment of once daily administration of risedronate (2.5 mg) has also been observed in patients with osteoporosis by many investigators [22–26]. A decrease in the parameters evaluating pain by VAS has been observed in 2–4 weeks after the start of the treatment with daily dosing [22, 23]. Similarly, improvement in the parameters evaluating pain by SF-36 or Japanese Osteoporosis Quality of Life Questionnaire (JO-QOL) has been observed in 4–12 months after the start of the treatment with daily dosing [24–26]. In this study, we observed a significant reduction of the value in the category of pain/discomfort in the EQ-5D after the first 12 weeks of weekly risedronate administration. Thus, the reduction of pain seemed to be consistent in both daily and weekly treatments of risedronate. This study confirmed the effect of pain with 17.5 mg risedronate treatment.

There are reports that risedronate shows a higher rate of improvement in the SF-36 bodily pain than etidronate and a lower rate of improvement than elcatonin [24, 26]. In this study, the increase in the total EQ-5D[utility] is associated with a decrease in pain/discomfort. Therefore, it is anticipated that the improvement of QOL by risedronate may be mainly the result of the effect of alleviation of pain. Multivariate analysis in this study did not find an effect of concomitant use of NSAIDs on either the total EQ-5D[utility] or the specific category of pain/discomfort. Thus, the effects of risedronate and NSAIDs on the alleviation of pain may be different in patients with osteoporosis.

Many factors including age, gender (being female), low BMI [27], low BMD [28, 29], previous fracture [30, 31], current smoking [32], alcohol intake [33], glucocorticoid use [34, 35], parent fractured hip [36], and rheumatoid arthritis [37, 38] have been reported to increase the fracture risk in patients with osteoporosis. Factors of age, previous fracture, and rheumatoid arthritis are also shown to affect QOL independently from consequent fracture. In this study, we found that age and glucocorticoid use affect the improvement of QOL in the early period of risedronate treatment, but previous fracture and rheumatoid arthritis did not reduce the effect on QOL. Thus, the relationships of fracture risk factors and QOL seem to be variable depending on the population of the subjects in the study. We found that FRAX values without BMD have a negative relationship with the changes in EQ-5D[utility] values. The efficacy of QOL improvement by risedronate treatment may be related to FRAX-integrated major risk factors in individuals.

Changes in QOL by risedronate treatment seem to depend on the comorbidities of lifestyle-related diseases in

patients with osteoporosis. In this study we found that comorbidity of ischemic heart disease and medication with glucocorticoid use blunted the changes in EQ-5D[utility] values by risedronate treatment. It has been reported that lifestyle-related diseases, such as diabetes, ischemic heart disease; hypertension, heart failure, arrhythmia, arteriosclerosis, and dyslipidemia, are associated with an increased risk of hip fracture [2–4, 8, 9]. This association is independent from decreasing BMD. In our study these comorbid diseases seemed to reduce the increase in EQ-5D[utility] values during osteoporosis treatment. We are not certain of the reason for the oppression of these comorbid diseases on the efficacy of QOL. The limited activities resulting from these lifestyle-related diseases could obscure the efficacy on QOL in the osteoporosis treatment by risedronate.

Among comorbidities of skeletal disorders other than osteoporosis, hip osteoarthritis was the confounding factor to affect the improvement of QOL by risedronate treatment. Other association of skeletal disorders such as degenerative spondylosis, spinal canal stenosis, and knee osteoarthritis did not have any influence on the response of the treatment by EQ-5D[utility] assessments. The reduction in QOL has been well confirmed in patients with osteoarthritis because of pain, limited range of motion of the affected joints, and associated muscle weakness [15, 19]. Blunting the response of QOL to treatment in patients with hip osteoarthritis seems to relate to the limited activities caused by joint dysfunction. No association with knee osteoarthritis as a factor to reduce the efficacy of risedronate on QOL may be the result of the wide degree of QOL effects by the disease.

The rates of drug-related AEs observed in this study (4.72 %) seem to be lower than the values (2.5 mg for 32.2 %, 17.5 mg for 24.9 %) reported in the regulatory approval of the study using weekly 17.5 mg risedronate dosing in Japan [39]. The difference in the rate of drug-related AEs is probably the result of the presence or absence of source document verification (SDV) by monitors. Additionally, it may also occur because the presence of abnormal clinical and laboratory findings has been entrusted to the investigator’s judgment. The most frequent drug-related AEs in this study were gastrointestinal disorders (3.56 %), which are generally known to be a drug-related AE of bisphosphonate use [40]. The mechanism of onset is considered to be dependent on the frequency of contact with the gastrointestinal mucosa [41]. The results in this study were similar to the safety profile in previous literature reports including studies using daily risedronate at 2.5 mg and 5 mg dosing [24, 39, 42–44].

Limitations of this study include that administration of risedronate 4 months later significantly increases the BMD of the lumbar spine (L1–L4) and the femur (neck and

total), and there is a report suggesting the possibility of reducing fracture risk [45]. Because the BMD data at final assessment were insufficient, the influence of BMD on QOL could not be sufficiently examined in this study.

In conclusion, we observed an improvement of QOL of patients with osteoporosis by risedronate 17.5 mg weekly dosing in daily practice. The improvements were blunted in patients with comorbidities. It is necessary to consider comorbidities before assessing the QOL effect in the treatment of osteoporosis.

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Conflict of interest None.

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