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The efficacy and tolerability of risedronate on bone mineral density and bone turnover markers in osteoporotic Chinese women: a randomized placebo-controlled study

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Abstract

Osteoporosis has become an important health problem in postmenopausal Asian populations as the prevalence of hip and vertebral fractures in some Asian countries has risen to approach that of Caucasian populations. Risedronate, a pyridinyl-bisphosphonate agent, is a potent inhibitor of bone resorption. Risedronate increases bone mineral density (BMD), reduces markers of bone turnover, and reduces the risk of fractures in Caucasian postmenopausal women. To determine the efficacy and tolerability of risedronate in Chinese, a multicenter, randomized, double blind, placebo controlled study was performed in Hong Kong. Sixty-five (65) postmenopausal osteoporotic Southern Chinese women, aged 67 ± 6 years, were randomly assigned to receive either risedronate 5 mg daily (n = 31) or placebo (n = 34) for 12 months. All women received calcium carbonate 500 mg daily and vitamin D 400 IU daily. Mean baseline BMD T-score at the spine and total hip was −3.4 and −2.6, respectively. A significant increase in spine BMD was already evident at month 3 of risedronate treatment (P < 0.001). Risedronate significantly increased BMD and reduced bone turnover markers as compared with placebo. The risedronate group had significant increase in BMD at 12 months at both the spine and hip when compared with the placebo group (L1–4 6.6% vs. 0.4%, P < 0.001; total hip 2.7% vs. 0.3, P < 0.0001; femoral neck 1.8% vs. 1.1%, P < 0.02; trochanter 4% vs. 1.1%, P < 0.0001, respectively). Significant changes in urine N-telopeptide (NTx) and serum osteocalcin were evident as early as 1 and 3 months, respectively, with risedronate treatment. No significant changes were seen in both BMD and bone markers in the placebo group. Risedronate was well tolerated without major adverse effects. We conclude that risedronate is an effective and well-tolerated agent for the treatment of postmenopausal osteoporosis in Asian population.

Keywords: Risedronate; BMD; Bone markers; Chinese

Introduction

Osteoporosis has emerged as an important metabolic bone disease globally. Based on population growth and the current incidence of hip fractures in Asia, it is estimated that by 2050, 50% of the world's hip fractures will occur in Asian women [1]. Epidemiological data revealed that even within Asia, the incidence of hip fracture varies with the highest in urbanized areas such as Hong Kong and Singapore [2]. The incidence of hip fractures in these two regions approaches almost that of Caucasian populations [2]. In Hong Kong, a secular trend is observed with the hip fracture incidence increased by about 2.5-fold over the past 3 decades [3]. About one third of postmenopausal Chinese women aged 70 or above in Hong Kong had evidence of morphometric vertebral fractures [4]. Prospective study performed on elderly subjects in Hong Kong revealed that fracture is among one of the three major illnesses that were

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associated with severe functional limitation, with the other conditions being stroke and dementia [5].

Early diagnosis and treatment of osteoporosis are the main steps to reduce fractures. Hormonal replacement therapy (HRT) had in the past been widely used in the prevention and treatment of postmenopausal osteoporosis. Although the recently published Women's Health Initiative (WHI) study confirmed the beneficial effect of HRT on fracture prevention, the use of conjugated equine estrogen and medroxyprogesterone acetate in patients with intact uterus was associated with an increased risk of coronary artery disease, pulmonary embolism, stroke, and breast cancer over an average study period of 5 years [6]. The use of HRT is currently suggested to be restricted to those without cardiovascular and breast cancer risks. Interestingly, acceptance of HRT varies between populations and is extremely low among Asian women. Even in the rather westernized population of Hong Kong, less than 3% of Chinese postmenopausal women had ever used HRT [7].

At present, bisphosphonates remain the mainstay of treatment for postmenopausal osteoporosis. Risedronate, a pyridinyl-bisphosphonate, had been shown to be effective in the prevention and treatment of postmenopausal osteoporosis. Among Caucasian women, risedronate reduces fractures at the spine by approximately 40% and at the hip by 30% (8–9). To determine the efficacy and tolerability in Asian population, a randomized placebo-controlled study was performed in postmenopausal Chinese women with osteoporosis.

Patients and methods

Patients

This was a multi-center, randomized, double-blind, placebo-controlled study. Postmenopausal Southern Chinese women were recruited from osteoporosis clinic of four centers in Hong Kong. These subjects were recruited if they were postmenopausal for 5 or more years with spine BMD at L1–4 <2.5 SD of the local peak young mean value. Subjects who had used estrogen or estrogen-related drugs in the preceding 12 months, bisphosphonates or fluoride in preceding 6 months, vitamin D supplementation in preceding 3 months, calcitonin or calcitriol in preceding 1 month, history of metabolic bone disease, impaired renal and liver function, history of recent major gastrointestinal disease or other major medical disease were excluded from the study. The patients were randomized to receive either risedronate (Actonel, Aventis Pharma) 5 mg daily or matching placebo to be taken on fasting in the morning for 1 year. All subjects received calcium carbonate 500 mg daily and Vitamin D 400 IU daily. The subjects were assessed for BMD measurement as well as fasting blood and urine markers of bone turnover. All patients gave informed consent and the protocol was approved by the Ethics Committee of each respective center.

Bone mineral density (BMD) measurements

BMD were measured at baseline and at 3, 6 and 12 months. The baseline BMD values were obtained from the mean of two measurements taken on the same day. BMD was measured at L1–4 and the hip region using dual-energy X-ray absorptiometry (DXA) (Hologic QDR 4500 plus, Hologic Inc., Waltham, MA, USA). All BMD measurements were done using one single machine by one single technician blinded to the randomization. The in vivo precision of the machine obtained from measuring five postmenopausal women four times over 2 weeks for lumbar spine, femoral neck, total hip, and trochanter was 1.2%, 1.5%, 1.5%, and 1.4%, respectively.

Lateral thoraco-lumbar spine was performed at baseline. To avoid influencing the precision and accuracy of subsequent spinal bone density evaluation, those with vertebral X-ray demonstrating physical abnormalities of the spine which would affect the lumbar BMD such as aortic calcifications, severe osteoarthritis, scoliosis, 2 or more lumbar spine fractures or 5 or more vertebral fractures were excluded from the study.

Biochemistries and biochemical bone markers

Fasting serum calcium, phosphorus, and total alkaline phosphatase (ALP) were measured using a Hitachi 747 random access analyzer (Boehringer, Mannheim, Germany). Fasting serum osteocalcin (Metra, CA, USA) and a 2-h fasting morning urine sample was collected for determination of urinary N-telopeptide/creatinine excretion (Osteomark, Ostex, Seattle, WA) at each visit. The interassay coefficient of variation for osteocalcin and NTx was 8.4% and 11.2%, respectively.

Statistics

The results were analyzed using an intention to treat approach (baseline measurement and at least one measurement on treatment with the last observation carried forward). Comparisons within and between groups were done by Student's t tests or analysis of variance (ANOVA) with repeated measures using SPSS program. All statistical tests were two-tailed, and a P value of <0.05 was considered significant.

Results

Bone mineral density

A total of 129 subjects underwent screening and 65 patients were finally recruited into the study and randomized