Effects of risedronate on lumbar bone mineral density, bone resorption, and incidence of vertebral fracture in elderly male patients with leprosy

ARIIKO KANAJI*, MASAAKI HIGASHI**, MASAKO NAMISATO**, MAKOTO NISHIO*, KENICHI ANDO* & HARUMOTO YAMADA*

*Department of Orthopaedic Surgery, Fujita Health University, Japan
**National Hansen’s Disease Sanatorium, Kuryu-Rakusen, Japan

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Summary  There is no well-established treatment for osteoporosis in male patients with leprosy, because no clinical trials have examined the efficacy of treatment on bone mineral density (BMD) or fracture incidence in such patients. The purpose of the present study was to evaluate the therapeutic effect on oral administration of risedronate in male osteoporotic patients with leprosy. Twenty-three male patients with leprosy, 63–87 years of age, were randomly divided into two administration groups: R group (risedronate, 2.5 mg/day, daily) and P group (placebo, daily). The BMD of the lumbar spine (L2–L4) was measured by dual-energy X-ray absorptiometry, and urinary cross linked N-telopeptides of type I collagen (NTX) were assessed at baseline, 6 months, and 12 months after treatment. There were no significant differences in age, body mass index, BMD, or urinary NTX levels at baseline between the two groups. In the present study, oral administration of risedronate apparently prevented vertebral fractures by increasing lumbar BMD and caused a significant reduction in urinary NTX levels, while oral administration of placebo did not increase the lumbar BMD and prevent vertebral fractures due to osteoporosis. The above findings suggested that oral administration of risedronate contributed to the prevention of vertebral fractures by suppressing bone resorption and increasing in lumbar BMD in the elderly male patients with leprosy.

Introduction

Osteoporotic fractures are widely recognized as a common and important cause of disability and death among patients with postmenopausal osteoporosis. In Japan, osteoporosis population is estimated at over ten million people.\(^1\) Spine fracture is very common in the elderly, with a lifetime risk of 37% for Japanese women aged 50. Hip fracture rapidly
increases among those at ages over 70, with a lifetime risk of about 14% for women aged 50 and 10-year fracture probability of 3% and 10% for women aged 70 and those aged 80, respectively. Osteoporosis is less common in men; however, Cooper et al. showed that approximately 25–30% of all hip fractures occur in men. Fujii also demonstrated that prevalence of osteoporosis reached about 20% for Japanese men in their late 70s. While osteoporosis in women is characterized by marked bone loss after menopause, osteoporosis in men is usually associated with diseases and drugs that threaten bone mass. Trovas et al. demonstrated that osteoporosis in men was associated with major risk factors, such as hypogonadism, excess of glucocorticoid therapy, and alcohol abuse. Peris et al. also showed aetiology in male osteoporosis. Among their 81 osteoporotic male patients, 63 had secondary causes of osteoporosis, including hypogonadism (12 men), corticosteroid therapy (10 men), and alcoholism (10 men).

Ishikawa et al. studied osteoporosis in Japanese patients with leprosy. That study demonstrated that low bone mineral density (BMD) in male patients with leprosy was due to hypogonadism and testicular atrophy by infection of Mycobacterium leprae. Moreover, Ishikawa et al. also showed that aging increased the incidence of osteoporosis in male patients with leprosy. In their report, the percentage of osteoporosis in male patients with leprosy was found to be 33.3% in the 50th, 58.3% in the 60th, 74.3% in the 70th, and 75.0% in the 80th decade. These findings demonstrated that suitable treatments to prevent the development of osteoporosis should begin immediately after the diagnosis of osteoporosis in elderly male patients with leprosy. However, management of male osteoporosis with leprosy has seldom been investigated, and few therapeutic trials have been performed in male patients with leprosy.

Recently, we examined a case of osteoporosis with leprosy treated by administration of alfalcaldol and risedronate. In our report, oral administration of risedronate was effective in increasing forearm BMD and reducing bone turnover. Risedronate is a potent bisphosphonate that inhibits osteoclast-mediated bone resorption. In postmenopausal women with osteoporosis, risedronate significantly reduces the incidence of major osteoporotic fractures, including those of the spine and hip. Therefore, we evaluated whether risedronate treatment prevents or reverses bone loss in male patients with osteoporosis. The present study demonstrated that oral administration of risedronate contributed to the prevention of vertebral fractures by remarkably suppressing osteoclast-mediated bone resorption and increasing lumbar BMD in the elderly male patients with leprosy.

Materials and methods

STUDY DESIGN

This randomized, double-blind, study was conducted at the National Hansen’s Disease Sanatorium between January 2001 and August 2003. The study protocol was approved by the institutional review board prior to initiation of the study, and all patients gave written informed consent before participating in this study, which was conducted in compliance with Good Clinical Practice and in accordance with the sprit of the Declaration of Helsinki.

Eligible patients were randomly assigned to receive risedronate (2.5 mg/day, daily) or placebo for 36 weeks. Tablet formations of risedronate and placebo were identical in appearance. Patients were requested to take one tablet immediately after arising every morning and not to take any food or beverage other than water for 30 min post-administration. Anti-inflammatory agents, vitamin D (1.0 µg daily), and calcium (1.0 g daily) supplements
were provided to all of the subjects; however, concomitant use of any other drugs known to affect bone metabolism were prohibited. Vitamin D and calcium supplementations were given once daily after supper. The patients and investigators, as well as the study coordinating staffs, were kept blind to the treatment assignments throughout the treatment period.

SUBJECT
The study was carried out in 23 male patients, 63–87 years of age, with leprosy. All of the patients were living in the National Hansen’s Disease Sanatorium, and were diagnosed with lepromatous leprosy by epidemiological, clinical, and histological findings. All of the subjects had long medical histories of neuralgia, numbness, and cold sensations in both legs. A total of 23 patients were also diagnosed with osteoporosis according to the criteria proposed by the Japanese Society for Bone and Mineral Research.10 Preliminary screening included their medical history, radiographic examination of thoracic and lumbar spine, blood and urine biochemical tests, and lumbar and forearm BMD measurements. The duration of the study was 12 months. After the start of treatment, lumbar BMD, and urine biochemical tests were assessed every 6 months, and radiographs and BMD measurements were performed as described below.

BIOCHEMICAL MEASUREMENT
Serum samples were analysed for calcium, inorganic phosphorus, total alkaline phosphates, total proteins, albumin, creatinine, and blood urea nitrogen by standard biochemical methods. Hormonal measurements including PTH-C, TSH, GH, 1α,25-dihydroxyvitamin D, calcitonin, cortisol, aldosterone, oestradiol, testosterone and osteocalcin were also performed in all the leprosy patients. Urinary crosslinked N-telopeptides of type I collagen (NTX) were measured by enzyme-linked immunosorbent assay.

BONE MINERAL DENSITY ASSESSMENT
Bone mineral density (BMD) of lumbar spine (L2–L4) in anteroposterior view was measured by dual-energy X-ray absorptiometry (DXA) using a Hologic QDR 1500W (Bedford, MA, USA).

ASSESSMENT OF VERTEBRAL FRACTURES
Vertebral fractures were evaluated using radiographs of thoracic (T8 centred) and lumbar vertebrae (L3 centred) that were taken from the anterior and lateral sides at baseline and 12 months after treatment. Vertebral fractures were identified in radiographs by experienced researchers and were confirmed using quantitative morphometry.10 Briefly, vertebral height was measured anteriorly (A), at the centre (C), and posteriorly (P). The presence of vertebral fractures was confirmed when (1) there was more than 20% reduction of vertebral height (A, C, and P) compared with the neighbouring vertebrae, and (2) the C/A or C/P ratio was less than 0·8, or the A/P ratio was less than 0·75.
STATISTICAL ANALYSIS

Data were expressed as mean ± SD. The unpaired t-test was used to compare the baseline characteristics and the number of incident vertebral fractures at the end of 12 months of treatment for the two groups. The significance of longitudinal changes in lumbar BMD, and urinary NTX level was determined by one-way analysis of variance (ANOVA). Furthermore, longitudinal changes in these two parameters were compared between the two groups by two-way ANOVA with repeated measurements. A significance level of \( P < 0.05 \) was used for all comparisons.

Results

PATIENT DISPOSITION

A total of 23 patients were included in the study (R group, \( n = 12 \) and P group, \( n = 11 \)). Among them, two patients were excluded from the safety analysis because of insufficiency of medication period (<21 days) and 21 patients (R group, \( n = 10 \) and P group, \( n = 11 \)) completed the planned schedule.

BASELINE CHARACTERISTICS OF SUBJECTS

The baseline characteristics of the 10 men in R group and 11 men in P group were similar. There were no significant differences in mean age, height, body weight, body mass index, or serum calcium and phosphorus levels at baseline between the two groups. The mean initial BMD of the lumbar spine was 0.482 g/cm\(^2\) in the R group and 0.489 g/cm\(^2\) in the P group, with no significant difference between the two groups. Testosterone levels at baseline of four men in the R group and five men in the P group were under the normal limits. However, there were no significant differences in the testosterone levels between the two groups. The normal limit for testosterone levels was 2.0–7.6 ng/ml, and the mean testosterone levels were 2.69 in the R group and 2.22 in the P group. The other hormone levels at baseline except testosterone were within normal limits in all subjects, with no significant difference between the two groups.

CHANGES IN LUMBAR BMD AND URINARY NTX

Figure 1 shows the longitudinal percent changes in lumbar BMD and urinary NTX. In the R group, the mean percent changes in lumbar BMD were 0.85 at 6 months and 0.84 at 12 months compared with baseline. The corresponding changes in urinary NTX levels were 79.3 at 6 months and 79.5 at 12 months. In the P group, the mean percent changes in lumbar BMD were 0.502 at 6 months and 0.515 at 12 months compared with baseline. The corresponding changes in urinary NTX levels were −22.3 at 6 months and −32.2 at 12 months. One-way analysis of variance (ANOVA) with repeated measurements showed no significant change in lumbar and urinary NTX levels in the P group, a significant increase in lumbar \((P < 0.05)\) and a significant decrease \((P < 0.05)\) in urinary NTX levels in the R group. Two-way ANOVA with repeated measurements showed a significant decrease in urinary NTX levels in the R group compared with the P group \((P < 0.001)\). The above findings demonstrated that oral administration of risedronate significantly increased lumbar BMD, with significant reduction.
in the urinary NTX, while oral administration of placebo did not achieve the significant increase in lumbar BMD.

**INCIDENCE OF VERTEBRAL FRACTURES**

At the end of treatment, plain radiographic examination of the thoracic and lumbar spine revealed evidence of incident vertebral fractures in the 10 patients in the R group and the 11 patients in the P group.

New vertebral fractures occurred during the 12-month treatment in 0.82 patients in R group and 1.88 patients in P group (Figure 2). The number of incident vertebral fractures per patient in R group was significantly lower than those in the P group ($P < 0.05$), suggesting that risedronate treatment was more effective to prevent incident vertebral fractures than treatment with oral administration of placebo.

**Discussion**

The results of the randomized drug-controlled study have shown that oral administration of risedronate contributed to the prevention of lumbar vertebral fractures due to osteoporosis. The present study also demonstrated that rapid and efficient suppression of bone resorption by this risedronate treatment resulted in preventing vertebral fractures due to osteoporosis in male patients with leprosy.

![Figure 1. Longitudinal percent change in lumbar BMD of the risedronate group (R group) and placebo group (P group).](image-url)
Osteoporosis, which is a well-recognized clinical manifestation of elderly patients with leprosy, was due to hypogonadism and testicular atrophy by infection of *Mycobacterium leprae*. During recent years, there has been accumulating evidence that androgen may play an important role in bone metabolism in male patients with osteoporosis. Several reports demonstrated that human osteoblast-like cells possessed androgen receptors, and that androgens were able to stimulate proliferation and differentiation of osteoblastic cells. Some clinical data have also suggested a stimulating effect of testosterone treatment on bone formation in hypogonadal male osteoporotic patients. Therefore, bone loss in androgen insufficiency may be caused by an impairment of bone formation. In line with this hypothesis, loss of androgen suppresses bone growth and reduces bone mass in male hypogonadal osteoporotic patients. On the other hand, loss of androgen results in an increase of osteoclast precursor formation in the bone marrow, leading to an increase in the number of osteoclasts on cancellous bone. The above findings demonstrate that the changes in bone marrow cells, including osteoblasts and osteoclasts, after loss of androgen can explain not only the well-established suppression of bone formation, but also the increase in the rate of bone resorption in elderly male osteoporosis patients with hypogonadism.

Risedronate is a potent bisphosphonate that inhibits osteoclast-mediated bone resorption. Harrington et al. demonstrated that risedronate significantly reduces the incidence of osteoporosis-related non-vertebral fractures within 6 months. Because of an antiresorptive effect on bone, risedronate is considered to be efficacious for high-turnover osteoporosis. Recently, we reported a case of osteoporosis with leprosy treated by administration of risedronate and alfacalcidol. In the leprosy patient, serum testosterone was very low (0.15 ng/ml) and the urinary NTx level was very high (90.3 nmol BCE/mmol Cr) before the treatment. However, a marked decrease in the urinary NTx level was demonstrated 1 and 6 months after the oral administration of risedronate and alfacalcidol. An increase in the forearm BMD was also shown 6 months after the treatment. In the present study, biochemical analysis demonstrated that increased bone resorption resulted in the marked low bone mass of the leprosy patients. Therefore, we surmised that risedronate treatment also had the potential to increase lumbar BMD and reduce the incidence of vertebral fractures in elderly male patients with leprosy. Our findings demonstrated for the first time that oral administration of risedronate resulted in a significant reduction of the incidence of vertebral fractures and increase in lumbar BMD by significantly suppressing osteoclast-mediated bone resorption in the elderly male patients with leprosy.

![Figure 2. Number of incident vertebral fractures. Data are expressed as mean ± SD. *P < 0.05 versus placebo group (2). There were 0.82 ± 0.30 per patient in the risedronate group (1) and 1.88 ± 0.56 in the placebo group (2). The difference was significant.](image-url)
In this report, we have shown the therapeutic efficacy of the risedronate treatment for male patients with leprosy. It is important to prevent the development of osteoporosis, and an established treatment is desirable for this purpose. The present study demonstrated that oral administration of risedronate could be a promising strategy for the prevention of vertebral fractures due to osteoporosis in elderly male patients with leprosy; however, a further study with a longer period of observation and a larger number of cases should be performed to evaluate the effects on this treatment.

References