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Original Article

Bone Mass Outcomes in Patients With Osteoporosis Treated With Risedronate After Alendronate Failure: a 12-Month Follow-Up Study

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Abstract

Oral bisphosphonates are the drugs most frequently used for the treatment of osteoporosis. Clinicians usually switch between these drugs in clinical practice based on differences in efficacy. We aim to investigate the reasons associated with switching between oral bisphosphonates and to evaluate bone mass response and the incidence of fractures 12 mo after the exchange in a cohort of patients with osteoporosis seen at a tertiary hospital. Patients with osteoporosis who switched between oral bisphosphonates between January 2007 and December 2014 were included. Bone mass measured by dual-energy X-ray absorptiometry and the incidence of fracture were evaluated. A total of 112 patients (73.1 yr old on average, 95.5% women, 98% postmenopausal) were included. All patients were taking alendronate at the time of the switch to risedronate. In 91 patients (81.3%), the following reasons for the exchange of medication were identified: bone loss (59.8%), adverse events (11.6%), and recent fragility fracture (10.7%). One year after the switch, bone densitometry revealed bone loss in 51 patients (45.5%), bone mass maintenance in 34 (30.4%), and bone mass gain in 27 (24.1%). No new vertebral fracture was detected and no nonvertebral fracture was reported in 12 mo of follow-up. Bone mass outcomes (gain, loss, or maintenance) were not associated with the reason for switching between oral bisphosphonates. Similarly, none of the parameters evaluated could predict good densitometric response (gain or maintenance) in this scenario. Our findings suggest that the use of risedronate should not be recommended in the scenario of treatment failure or adverse events following the use of alendronate.

Key Words: Alendronate; bone mineral density; osteoporosis; risedronate; treatment failure.

Introduction

Antiresorptive drugs and medications with anabolic effects are available and efficiently reduce the risk of fractures associated with osteoporosis *(1)*. Bisphosphonates are the most widely used drugs in the treatment and prevention of osteoporosis *(2)*. Synthetic analogs of pyrophosphate, new amino bisphosphonates, bind to the mineralized bone matrix, are incorporated into the osteoclasts during the bone resorption process, and inhibit farnesylpyrophosphate synthase, resulting in increased apoptosis and reduction in the resorptive activity of these cells *(3)*. The efficacy and highly favorable safety profile of these drugs are key elements in the management of bone fragility *(4)*.

Several well-designed placebo controlled, randomized clinical trials and meta-analyses have shown a significant reduction in fracture risk in patients with osteoporosis receiving oral bisphosphonates. Alendronate was the first bisphosphonate approved for the treatment of

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osteoporosis (5). Pivotal trials have demonstrated that the use of alendronate in postmenopausal women with osteoporosis was associated with a significant reduction in the risk of vertebral and nonvertebral fractures, including hip fracture (6). Studies with a similar design have demonstrated the effectiveness and safety of risedronate (7,8). Some other studies have demonstrated the efficacy of risedronate in reducing vertebral and nonvertebral fractures, including hip fractures (9,10).

Direct comparison studies on the efficacy of the various drugs approved for the management of osteoporosis are rare, specially having the fragility fracture as the main outcome. Alendronate has been compared to risedronate in an animal model with very similar results in bone strength and microdamage accumulation (11). In postmenopausal women with osteoporosis, alendronate was associated with higher reduction in bone resorption markers and higher bone mineral density (BMD) gains as compared to risedronate (12). On the other hand, the potential superiority of 1 drug over another has not been conclusively demonstrated (13,14). Reductions in the relative risk of radiological vertebral fractures with the use of alendronate vary between 41% and 49% at 3 yr of continuous use. Risedronate significantly reduced the relative risk of radiological vertebral fractures by 61%–65% at 1 yr. Direct comparisons of those results are not advisable because the studies included diverse populations with significant differences in baseline fracture risk. Multicenter study data also have shown that protection against clinical vertebral fractures and nonvertebral fractures with risedronate occurs early at 6 mo of treatment, an effect not demonstrated with other bisphosphonates (15,16).

The switching between these drugs in the management of patients with osteoporosis, very common in clinical practice, has been grounded in the frequency of adverse events (also not different between these drugs) and the availability of these medications. The present study aimed to investigate the reasons associated with switching between oral bisphosphonates in clinical practice and to evaluate bone mass response and fragility fracture incidence in patients undergoing sequential use of oral bisphosphonates.

Methods

We conducted an observational retrospective cohort study from January 2007 to December 2014 using patients of both genders seen at the osteoporosis outpatient clinics at the Rheumatology Division, Universidade Federal de São Paulo (UNIFESP), a tertiary public health unit in Brazil. Patients treated with oral bisphosphonates who for any reason switched to another oral bisphosphonate during the course of their management were selected from the electronic medical chart database. Cases had to be considered treatment failures (bone loss or fragility fracture) or reported as adverse events. For the purpose of the present study, treatment failure was defined as a significant decrease in BMD (higher than the least significant change [LSC]) or an incident fragility fracture. Patients had to be adherent to the treatment before switching, vitamin D sufficient (25(OH)D serum concentration of ≥30 ng/mL), and without secondary causes of osteoporosis (hyperparathyroidism, thyroid dysfunction, hematological conditions, Cushing's syndrome, hypercalciuria, etc.). Patients who used other therapies (raloxifene, zoledronic acid, denosumab, strontium ranelate, or teriparatide) in the interval between the 2 oral bisphosphonates were excluded. All participants were contacted and gave informed consent before inclusion in the study. UNIFESP's ethical committee approved the study protocol.

As routine care in our outpatient clinics, patients had bone densitometry at the lumbar spine and proximal femur using dual-energy X-ray absorptiometry technique (DPX-MD Plus, GE Lunar, Madison, WI) performed annually. The LSC for dual-energy X-ray absorptiometry in our center is 0.030 g/cm^2 for the proximal femur and 0.018 g/cm^2 for the lumbar spine. Diagnosis of osteoporosis as well as the comparison between bone scans were based on the International Society of Clinical Densitometry 2007's recommendations (17). BMD increments higher than the LSC were considered bone mass gain, whereas BMD reductions over the LSC were categorized as bone mass loss. Bone mass maintenance occurred when BMD difference between scans was lower than the LSC.

Vertebral fracture survey was performed at annual intervals (before and 12 mo after the oral bisphosphonate switch). Anteroposterior and lateral plain radiographs of the thoracic and lumbar spine were systematically performed to survey for vertebral fractures. Genant's criteria were used to classify the type and severity of prevalent spinal deformity (18). Deformities grade II or higher were considered as vertebral fractures.

BMD measurements and vertebral radiographs are taken before medication and then yearly thereafter as routine care in UNIFESP's outpatient clinics.

Nonvertebral osteoporotic fractures were recorded from medical charts.

Statistical Analysis

Data are presented as mean ± standard deviation. Student's *t* test was used to compare variables with normal distribution, whereas chi-square or Fisher's exact test was used to compare prevalence between groups of patients. The comparison of variables with non-normal distribution was performed by nonparametric tests (Mann-Whitney's test and Spearman's correlation test). A multiple logistic regression analysis was performed to determine the association between bone mass outcomes (bone mass gain, loss, or maintenance) tailored to the presence of relevant independent variables. Odds ratio with confidence interval of 95% were calculated. The Statistical Package for Social Science, SPSS 12.0 (IBM, Armonk, NY), was used for all the analyses. Significance level was set as $p < 0.05$.