Original Article

Short-Term Risedronate Treatment in Postmenopausal Women: Effects on Biochemical Markers of Bone Turnover

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Abstract. The development of new biochemical markers has made it possible to assess the effects of therapeutic agents on bone turnover more rapidly and precisely. In this early phase II study, we analyzed the effects of short-term, high-dose treatment with risedronate, a potent pyridinyl bisphosphonate, on markers of bone resorption and formation. Resorption markers included urinary free deoxypyridinoline (D-Pyr) crosslinks, N-terminal telopeptide (NTX) and C-terminal telopeptide (CTx) type I collagen crosslinks. Bone formation markers included osteocalcin (OC), bone-specific alkaline phosphatase (BSAP) and the C-terminal peptide of type I procollagen (PICP). All three resorption markers showed rapid, significant (p<0.05) decreases from baseline following daily administration of 30 mg risedronate for 2 weeks. The mean decreases at 2 weeks were 28% for D-Pyr, 61% for NTx and 73% for CTx, respectively. Over the next 10 weeks after treatment, D-Pyr approached baseline while NTx and CTx remained well below baseline values. The markers of bone formation showed little change during therapy but decreased significantly at 4–10 weeks after therapy—an expected outcome of bisphosphonate therapy. Moreover, there was a significant correlation between the early effects on bone resorption markers and the delayed effects on formation markers. This study demonstrates that the approved dose of risedronate (30 mg/day) for Paget’s disease is effective at decreasing bone turnover after 2 weeks of treatment, as observed by the sensitive response of bone turnover markers.

Keywords: Bisphosphonate; Bone markers; Bone-specific alkaline phosphatase; Osteocalcin; Resorption; Risedronate; Telopeptides

Introduction

The discovery of biochemical markers of bone formation and resorption has made it possible to assess the relationships between bone turnover, bone mass, and bone loss [1,2]. In addition, these markers can be used to assess the effectiveness of new drugs much more rapidly than can be done by measuring changes in bone mass [1,3,4]. Clinical goals are to use early changes in bone markers as predictors of the subsequent changes in bone mass and fracture risk in osteoporosis, or of therapeutic response in osteolytic disorders, such as Paget’s disease, or malignancy [4–7]. This approach is promising, but there are only limited prospective data available, and proof of this concept will require not only more studies but also a careful analysis of the relative response of different markers to different therapeutic agents.

Risedronate [1-hydroxy-2-(3-pyridinyl)ethylidene bisphosphonic acid monosodium salt] is a new bisphosphonate with a strong antiresorptive effect due to inhibition of osteoclastic activity. This potent pyridinyl bisphosphonate, currently under clinical development for the treatment and prevention of postmenopausal osteoporosis and other bone metabolic bone diseases, has been shown to be a safe and effective antiresorptive agent in Pagetic, hypercalcemic and osteoporotic patients [5,7–12].

This early phase II study of the effect of short-term risedronate treatment on biochemical markers of bone
turnover in early postmenopausal women was designed to assess the responsiveness of bone-specific markers in monitoring bone turnover and to provide information concerning the utility of biochemical bone markers in further clinical studies. The effects of 2 weeks of oral risedronate treatment at the dose of 30 mg/day (gelatin capsule formulation), the dose currently recommended for the treatment of Paget’s disease, were assessed. A full panel of markers was used to measure the pharmacodynamic effects of risedronate on both bone resorption and formation, and to compare the relative utility of different markers of bone turnover. Three urine immunoassays were used to compare markers of bone resorption, i.e., the free deoxypyridinoline crosslink (D-Pyr) and the type I collagen N-terminal telopeptide (NTx) and C-terminal telopeptide (CTX) crosslinks. Three markers of bone formation were also assessed: osteocalcin (OC), bone-specific alkaline phosphatase (BSAP) and the C-terminal peptide of type I procollagen (PICP).

Materials and Methods

This single-center, open-label study was conducted at the University of Connecticut Health Center after obtaining approval from the Institutional Review Board and the informed consent of participants. Healthy women, 1–7 years postmenopausal, with FSH >20 mU/ml, estradiol <40 pg/ml, normal liver function and normal hematologic values, were enrolled. Subjects with radiographic evidence of vertebral fractures, or bone mineral density (BMD) more than 2 SD below young adult normal premenopausal mean BMD (i.e., T-score < −2), or who were being treated with medications known to affect bone metabolism, were excluded. Subjects were evaluated three times before initiating therapy (weeks −4, −2, and time 0 [baseline]); during the 2 week treatment (at weeks 1 and 2); and at 2, 4 and 10 weeks after treatment (weeks 4, 6 and 12 of the study).

All subjects were instructed to consume a diet that maintained their current calcium intake and to take three 10 mg risedronate gelatin capsules once daily for 2 weeks. (The gelatin capsule formulation was an early risedronate dosage form that has since been replaced by a film-coated tablet.) This was followed by a 10 week post-treatment period. To maximize absorption, subjects were instructed to: (1) swallow the risedronate capsules with at least 8 ounces (235 ml) of water 2 h before or after food, and not to take the drug with milk or with calcium-supplemented liquids; (2) avoid taking the study medication within 2 h of consuming vitamins or antacids that contained calcium, iron, magnesium or aluminum; and (3) remain upright for at least 1 h following administration of risedronate.

Measurements of bone turnover, physical examination and medication history were obtained before study initiation and adverse reactions were monitored at all visits during and after treatment. Blood and second-voided urine samples were obtained before 1000 hours. Subjects had fasted for at least 8 h. Risedronate was taken after the blood and urine samples had been obtained. In addition to the bone markers, biochemical measurements at each visit included fasting serum and urinary calcium, phosphorus and creatinine. Intact parathyroid hormone (PTH), calcitomin, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were measured at each screening visit, at time 0, and at 2 and 6 weeks. BMD was used to assess entry criteria, not as an efficacy endpoint. Because the treatment phase lasted only 2 weeks, BMD change was not an appropriate endpoint.

OC was measured using three different double-antibody assays. Two of the assays (OC-1, ELISA-Osteo, CIS-US, Bedford, MA, and OC-2, OsteoHuman, Nichols Diagnostics, San Juan, Capistrano, CA) are reported to measure both intact and large N-terminal fragments, while the third (OC-3, Novocalcin, Metra Biosystems, Palo Alto, CA) is reported to measure only the intact protein. Nevertheless the absolute values for OC-2 and OC-3 were similar and lower than the value for OC-1, using the manufacturers’ standard curves. Single-antibody assays were used to quantitate BSAP (Ostase, Hybritech, San Diego, CA) and PICP (Prollagen C, Metra Biosystems). Free D-Pyr (Pyrilinks D, Metra Biosystems), NTx (Osteomark, Ostex, Seattle, WA) and CTx (Crosslaps, Osteometer, Copenhagen, Denmark) were analyzed using single-antibody assays and corrected for creatinine concentration. Intra-assay coefficients of variation for the markers of bone turnover ranged from 6% to 10%. All assays of collected samples from each subject were performed at the same time. All marker assays were performed in duplicate in the Core Laboratory of the General Clinical Research Center at the University of Connecticut Health Center and repeated if the pairs did not agree within 10%. The mean of the two closest values was then used. Repeated assays for NTx and D-Pyr were generally consistent, but one set of repeated assays for CTx showed aberrant values, possibly related to a problem with the assay kit employed. Hence CTx pairs which differed by up to 20% were used to obtain the mean. Vitamin D metabolites were measured at the University of Southern California and vitamin D binding protein was measured at the University of Pennsylania. All other assays were carried out at the Nichols Institute (San Juan Capistrano, CA).

Statistical analyses of the reproducibility of the baseline assays were carried out using a univariate repeated measures analysis of variance (ANOVA). Response to treatment was assessed by the percent changes from baseline for each marker. The mean of the three pretreatment measurements was used as the baseline value. The correlation between markers was determined at each time point, using the conditional bivariate normal correlation model.

Results

The characteristics of the subject population are summarized in Table 1. Of the 15 subjects who enrolled,