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Original Article

Bone turnover rate and bone formation/resorption balance during the early stage after switching from a bone resorption inhibitor to denosumab are predictive factors of bone mineral density change

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Abstract

Objectives: This study aimed to investigate the correlation between bone mineral density (BMD) and the turnover rate [$\sqrt{(MoMf^2 + MoMr^2)}$, multiple of median formation (MoMf) was calculated as bone-specific alkaline phosphatase (BAP) value/18.6 and multiple of median resorption (MoMr) as tartrate-resistant acid phosphatase 5b (TRACP-5b) value/463] and the balance (MoMf/MoMr) and to compare differences in therapeutic effects evoked by differences in previous treatments.
Methods: In 51 osteoporotic women treated with bisphosphonates (BPs) or selective estrogen receptor modulators (SERMs), BMD was measured at 0, 24, and 48 weeks after denosumab administration. The values of BAP and TRACP-5b were measured at 0, 4, 12, 24, 36, and 48 weeks.
Results: The turnover rate decreased at week 4 and decreased further at week 12. The balance indicated a relative predominantly formative state at week 4. This balance became higher in the SERM group than in the BP group at week 4. A correlation was observed between the rate of BMD change and turnover rate at weeks 0 and 4.
Conclusions: It is necessary to evaluate the turnover rate and balance to determine the therapeutic effect of denosumab, which induces dissociation between the trends in the bone turnover markers. Turnover rate and balance during the early stages of denosumab treatment may be predictive factors of BMD. When switching from bone resorption inhibitors to denosumab, it was necessary to consider the beginning values that were affected by the previous treatment. The state of relative anabolism is greater at 4 weeks when the previous treatment involved SERMs rather than BPs.

Keywords: Osteoporosis; Denosumab; Bone mineral density; Bone-specific alkaline phosphatase; Tartrate-resistant acid phosphatase 5b

1. Introduction

Denosumab is a powerful inhibitor of bone resorption and is reported to increase bone mineral density (BMD) and decrease the incidence of fragility fractures [1–5]. BMD and bone turnover markers (BTMs) have been used to evaluate the therapeutic effects of denosumab. BTMs have often been assessed by measuring either bone formation or resorption markers or by separately evaluating both parameters [1–6]. However, during these assessments, it was difficult to assess bone turnover in terms of both bone formation and resorption, and it was also difficult to observe the balance between bone formation and resorption. Dissociation has been observed between bone formation and resorption markers immediately after treatment with denosumab [2,6,7]. In these cases, there is a possibility of erroneously evaluating bone metabolism without the simultaneous evaluation of bone formation and resorption markers. Furthermore, it is necessary to evaluate the balance between these two markers to determine therapeutic effects. Bieglmayer and Kudlacek [8] introduced a method for visually presenting the rate of bone turnover (referred to as

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turnover rate hereafter) with the balance between bone formation and resorption (referred to as balance hereafter) by depicting the levels of bone formation and resorption markers two-dimensionally on a graph. In this method, it becomes easy to evaluate the turnover rate and balance.

The present pilot study hypothesized that the simultaneous evaluation of bone formation and resorption markers is useful in determining the efficacy of denosumab treatment during which bone formation and resorption dissociation occur. The purpose of the study was to investigate whether future changes in BMD can be predicted from the early turnover rate and balance and to compare differences in therapeutic effects observable in BMD and BTMs evoked by differences in previous treatments.

2. Methods

Subjects were diagnosed with primary osteoporosis according to the revised Japanese diagnostic criteria for primary osteoporosis (Primary osteoporosis is diagnosed based on the presence of any fragility fractures at various sites, including spine and proximal femur or another fragility fractures with BMD < 80% young adult mean (YAM). If there is no fragility fracture, BMD ≤70% of YAM or ≤−2.5 standard deviation (SD) is also diagnosed as primary osteoporosis) [9]. The study was approved by the ethics committee at the Asahi General Hospital. Fifty-one postmenopausal women (68−92 years of age, mean age: 80.9 ± 6.6 years) were recruited, each with reduced lumbar vertebral or femoral BMD compared with that present 24 weeks prior (lumbar vertebral BMD was reduced in 27 subjects and femoral BMD was reduced in 30 subjects), irrespective of whether they were receiving treatment with bisphosphonates (BPs) or selective estrogen receptor modulators (SERMs). Of these, 44 women took alfacalcidol [BP and alfacalcidol (n = 24) and SERM and alfacalcidol (n = 20)] and one took SERM and calcium aspartate. The previous treatment was discontinued for all subjects, and they were administered 60 mg of denosumab every 24 weeks as treatment for osteoporosis. In addition, subjects were administered a combined formulation containing calcium (305 mg), natural vitamin D_3 (5.0 μg), and magnesium (15 mg). Subjects receiving medications that could influence bone metabolism, those with hypocalcemia or secondary osteoporosis, and those with a history of surgery on the lumbar vertebrae (L2−4) were excluded. All recruited subjects showed no fracture within 100 days of the study initiation.

BMD of L2−4 and the left proximal femur (total) was measured by dual-energy X-ray absorption (DXA, Discovery A, Hologic, Inc, Bedford, MA, USA, Coefficient of variations are 1% at both the AP spine and the total hip) at the beginning of denosumab administration (week 0) and at weeks 24 and 48. Further, BMD of subjects with surgery or coxarthrosis of the left hip joint was measured on the right proximal femur if there was no surgery or coxarthrosis of the right hip joint. The values of bone-specific alkaline phosphatase (BAP) and tartrate-resistant acid phosphatase 5b (TRACP-5b) were measured at 0, 4, 12, 24, 36, and 48 weeks after the initial administration of denosumab. These measurements were divided by median values for untreated postmenopausal women with osteoporosis (18.6 μg/L for BAP and 463 mU/dL for TRACP-5b) to determine the multiple of median formation (MoMf, measured BAP value/18.6) and multiple of median resorption (MoMr, measured TRACP-5b value/463). These values were then plotted onto a graph using the Bieglmayer method [8,10]. The turnover rate was calculated as $\sqrt{(MoMf^2 + MoMr^2)}$ and the balance as MoMf/MoMr. There was no washout period between the discontinuation of the previous treatment and initiation of denosumab administration.

IBM SPSS Statistics version 20J (IBM, Armonk, NY, USA) was used for all statistical analyses. Time-dependent changes were compared using the Wilcoxon signed rank test, and differences between the two groups were evaluated using the Mann−Whitney test. Spearman's rank correlation coefficient was used to determine correlations between the two groups. The probability ellipse for the two-dimensional normal distribution was obtained from an electronic source. (This probability ellipse program was made by Shigenobu Aoki who resigned from the assistant professor at Gunma University society information department. http://aoki2.si.gunma-u.ac.jp/R/scatter.html) and created using Microsoft Excel.

3. Results

Ten of the 51 subjects were excluded for the following reasons: six failed to appear for follow-up at the hospital, two experienced fractures, one died, and one underwent articular surgery. The remaining 41 (68−92 years of age) were included for analysis. Previous treatments involved BPs for 22 subjects (BP group: alendronate, 17 subjects; risedronate, one subject; minodronic acid, three subjects; and ibandronate, one subject) and SERMs for 19 subjects (SERM group: raloxifene, 17 subjects and bazedoxifene, two subjects; Table 1).

3.1. Changes in BMD

Lumbar BMD increased in 35 subjects (BP group, 19 subjects and SERM group, 16 subjects) at week 24 and in 33 subjects (BP group, 16 subjects and SERM group, 17 subjects) at week 48 compared with that at week 0. Femur BMD increased in 26 subjects (BP group, 12 subjects and SERM group, 14 subjects) at week 24 and in 31 subjects (BP group, 15 subjects and SERM group, 16 subjects) at week 48 compared with that at week 0. The percent change of increase in lumbar BMD at weeks 24 and 48 were 4.8 ± 4.2% and 4.8 ± 5.9%, respectively, whereas those of femur BMD were 5.8 ± 16.3% and 6.7 ± 17.2%, respectively. The values of both parameters significantly increased compared with those at the beginning of the treatment, with the increases exceeding the least significant change (Table 2).

3.2. Changes in turnover rate and balance

With the exception of BAP values at week 4, both BAP and TRACP-5b values significantly changed beyond a minimum significant change [11] during the treatment period