Changes in Bone Resorption Marker at One Month Predict Changes at Six Months in Patients Treated with Alendronate

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Abstract

Ninety-nine postmenopausal Japanese women were evaluated to assess whether changes at one month in urinary NTX bone resorption marker as a result of alendronate treatment enable prediction of changes at 6 months. The percentage change at one month significantly correlated with that at 6 months ($R^2 = 0.290$, $P = 0.0001$) and predicted the changes at 6 months with sensitivity 72.2%, specificity 60.0%, positive predictive value 87.7%, and negative predictive value 35.5%, respectively. This study demonstrated that changes in bone resorption marker at one month could be used as a reliable method to monitor the effects of alendronate treatment, and to predict the response at six months.

Key words Osteoporosis, Alendronate, Bone resorption marker, Urinary NTX, Bisphosphonate

Introduction

Recent studies have indicated that oral administration of alendronate, a bisphosphonate, can prevent fracture in patients with osteoporosis.1–5 Although bone mineral density (BMD) is an essential tool for estimating fracture risk in untreated populations, changes in BMD may explain only a small part of fracture risk reduction.6 Accelerated bone resorption marker also independently contributes to fracture risk. Urinary cross-linked N-telopeptides of type I collagen (NTX), one of bone resorption marker, has been shown to reduce substantially after 6 months of treatment,7–10 representing a decrease in fracture risk as a result of bisphosphonate treatment.11 However, one of the most critical problems in the treatment of osteoporosis is that because there is no reliable method for early monitoring of the response to treatment, patients do not continue to adhere to motivation.

Materials and Methods

Ninety-nine postmenopausal Japanese women aged 67.1 ± 8.8 years of age (mean ± SD, range; 46–84) were recruited. No clinical or laboratory evidence of confounding by systemic manifestation of any disease was observed for these patients. All patients satisfied the following preconditions: (1) at least 5 years since menopause, (2) lumbar spine BMD of more than 2.5 SD below the young adult mean of normal Japanese women, (3) no illness and receiving no medication that might affect bone mineral metabolism, (4) no clinical fracture within 6 months, and (5) receiving medication with alendronate (5 mg/day) and having taken all of...
the tablets prescribed for the first month and at least 90% of the tablets prescribed for each of the following 6 months. Medication was taken with 180 ml of water in the morning 30 minutes before breakfast or a beverage.

To ascertain a baseline, urinary NTX, corrected for creatinine, was measured using second morning void urine samples at one month and at six months after the start of alendronate treatment. According to the guidelines of the Japan Osteoporosis Society, the cut point (minimum significant change, MSC) for urinary NTX is determined as a decrease from baseline of 35%.

The relationships between changes from baseline at one month and changes from baseline at 6 months were examined using simple regression. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were used to assess whether the change from baseline at one month could be used to predict the change from baseline at 6 months in individual patients. PPV and NPV were calculated according to the probability of a positive response in urinary NTX at 6 months in patients with a decrease to below the cut point at one month, and the probability of a negative response in urinary NTX at 6 months in the patients without a decrease to below the cut point at one month, respectively.

### Table 1 Number of cases that showed MSC or not at one and 6 months

<table>
<thead>
<tr>
<th></th>
<th>1 month</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>MSC</td>
<td>no MSC</td>
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<tr>
<td>6 months</td>
<td>57 cases</td>
<td>22 cases</td>
</tr>
<tr>
<td>no MSC</td>
<td>8 cases</td>
<td>12 cases</td>
</tr>
<tr>
<td>Total</td>
<td>65 cases</td>
<td>34 cases</td>
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</tbody>
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(MSC: minimum significant change)

<table>
<thead>
<tr>
<th>Sensitivity: 57/79 = 72.2%</th>
<th>Positive Predictive Value: 57/65 = 87.7%</th>
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<tr>
<td>Specificity: 12/20 = 60.0%</td>
<td>Negative Predictive Value: 12/34 = 35.3%</td>
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Results

Urinary NTX values were 57.2 ± 27.7 nmol BCE/mmol • Cr (mean ± SD) at baseline, 31.8 ± 16.0 at one month, and 26.2 ± 17.1 at 6 months (Fig. 1). The percentage change in NTX from baseline at one and six months was −38.6% ± 31.9 and −48.5% ± 25.9 (mean ± SD), respectively (Fig. 2). The percentage change from baseline at one month significantly correlated with the percent change from baseline at 6 months (R² = 0.290, P < 0.0001; Fig. 3). Of 99 patients, 65 (65.7%) and 79 (79.8%) patients showed MSC at one month and 6 months, respectively. A change from baseline at one month predicted the change from baseline at 6 months with sensitivity 72.2% and specificity 60.0%. PPV indicated the probability of 87.7% that urinary NTX would remain below the cut point at 6 months if this had been the case at one month. Conversely, NPV indicated a 35.3% probability that urinary NTX would not decreased below the cut point at 6 months if urinary NTX had not decreased below the cut point at one month (Table 1).

Discussion

Although urinary NTX is known to be a reliable monitor in the treatment of osteoporosis, there is no previous report on whether change in urinary NTX at one month can predict the change in urinary NTX at six months. In this study, we observed that urinary NTX decreased significantly at one month, and that the magnitude of the decrease at one month was similar to that at six months. Moreover, the change from baseline in urinary NTX at one month significantly correlated with that at six months. The PPV was also high indicating a strong probability that urinary NTX would continue to be below the cut point at six months if it had been so at one month. However, compared to the PPV, the NPV at six months was a lower percentage, suggesting that a late response to alendronate treatment may occur in some cases.

This study clearly demonstrated that changes at one month in the biochemical marker of bone turnover NTX could be used as a reliable method to monitor the effects of alendronate treatment and to predict the response to treatment at six months.

These results suggest that patients with a decrease in urinary NTX at one month below the cut point should be encouraged to continue the alendronate treatment. If no decrease in urinary NTX below the cut point is observed at one month, it is advisable to ascertain whether or not the patient had been taking the medication correctly (with 180 ml of water in the morning, 30 minutes before breakfast or a beverage). Even if medication had been taken correctly, the patient should be advised to continue the treatment to the 6-month point because 64.7% (22/34) of patients without a decrease in urinary NTX below the cut point at one month showed a positive result at six months (Table 1).

Since the aim of treatment for osteoporosis is the prevention of osteoporotic fracture, the endpoint of treatment should be the prevention of fracture. In this study, fracture was not the endpoint due to the low incidence of fractures in one month; however, recent studies have suggested that the reduction of fracture risk is more dependent on the decrease of bone resorption marker than the increase of BMD.12,13 Results of longer-term studies involving large populations are needed to determine whether early changes in biochemical markers can also be used as predictors of fracture risk.

References

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