J Bone Miner Metab (2005) 23:333–336
DOI 10.1007/s00774-005-0609-4

CASE REPORT

Junichi Takada · Kousuke Iba · Toshihiko Yamashita

Low dose of oral alendronate decreases bone turnover in Japanese patients with Paget's disease of bone

Received: October 25, 2004 / Accepted: January 11, 2005

Introduction

Paget's disease of bone is a disorder showing chronic abnormality of bone turnover. Paget's disease is common in Europe, North America, Australia, and New Zealand, but is rare in Asia [1]. Alendronate, one of the bisphosphonates, is now widely used for the treatment of Paget's disease, and numerous studies have demonstrated the efficacy of alendronate for this purpose [2–5]; however, alendronate is not licensed in Japan for the treatment of Paget's disease. The dose of a bisphosphonate used for the treatment of Paget's disease is higher than that used for the treatment of osteoporosis. However, there has been no report on the appropriate dose of alendronate for the treatment of Paget's disease in Japanese patients.

We report two cases of Paget's disease in Japanese patients treated with a low dose of alendronate (5 mg per day, orally) for 6 months. Marked reduction of bone turnover was seen in both patients, and the reduction of bone turnover lasted for 1 year after treatment had been discontinued.

Case 1

A 66-year-old man presented with low back pain. There was no notable disease in his past medical records. Radiography confirmed pagetic changes, as well as osteolytic and sclerotic changes, in a local area of the left acetabulum and half of the ilium, and the pubic bone, while whole-body bone scintigraphy with ^{99m}Tc (technetium) showed hot spots in the left acetabulum, half of the ilium, and the pubic bone. Laboratory findings reflected an increase of bone turnover; that is, bone formation was reflected by increased levels of serum total alkaline phosphatase (T-ALP; 1344 IU/l; normal range, 110–370 IU/l) and serum bone-specific alkaline phosphatase (BAP; 129.2 U/l; cutoff range in Japanese men, ≤44.0 U/l). Bone resorption was reflected by increased levels of urinary N-terminal telopeptide of type I collagen (NTX; 213 nmol bone collagen equivalent [BCE]/mmol·creatinine [Cr]; cutoff range in Japanese men, ≤66.2 nmol BCE/mmol·Cr) and deoxypyridinoline (DPD; 12.3 nmol/mmol·Cr; cutoff range in Japanese men, ≤5.6 nmol/mmol·Cr; Fig. 1). The diagnosis of Paget's disease was made on the basis of results of radiography, bone scintigraphy, and laboratory examinations. Because Paget's disease is rare in Japan, open biopsy was done to confirm the diagnosis. Histology showed a mosaic structure of resorption and formation, and there was no evidence of a malignant neoplasm or other bone disease.

The patient was treated with alendronate, at 5 mg per day, orally, and alphacalcidol (1.0 μg/day), and daily calcium intake was set at 1000 mg to prevent a secondary increase in parathyroid hormone (PTH). Nonsteroidal anti-inflammatory drugs had not been taken. The low back pain disappeared within 1 month. Six months after the start of alendronate treatment, bone turnover had reached a normal level (T-ALP, 157 IU/l; BAP, 14.5 U/l; NTX, 14.4 nmolBCE/mmol·Cr; DPD, 2.3 nmol/mmol·Cr). Radiography and computerized tomography at 6 months did not show any changes. There was no correlation between the disappearance of the low back pain and the decrease of bone markers. Treatment was then discontinued, and the decrease in bone turnover lasted for 1 year (Fig. 1).

Case 2

A 68-year-old woman complained of low back pain and excessive warmth over bone. She had nothing notable in her past medical records. Radiography showed pagetic changes, and whole-body bone scintigraphy with ^{99m}Tc showed a hot spot in 90% of the left pelvis. Laboratory findings revealed

J. Takada (✉) · K. Iba · T. Yamashita
Department of Orthopaedic Surgery, Sapporo Medical University, South-1, West-16, Chuo-ku, Sapporo 060-8543, Japan
Tel. +81-11-611-2111; Fax + 81-11-641-6026
e-mail: jtakada@sapmed.ac.jp

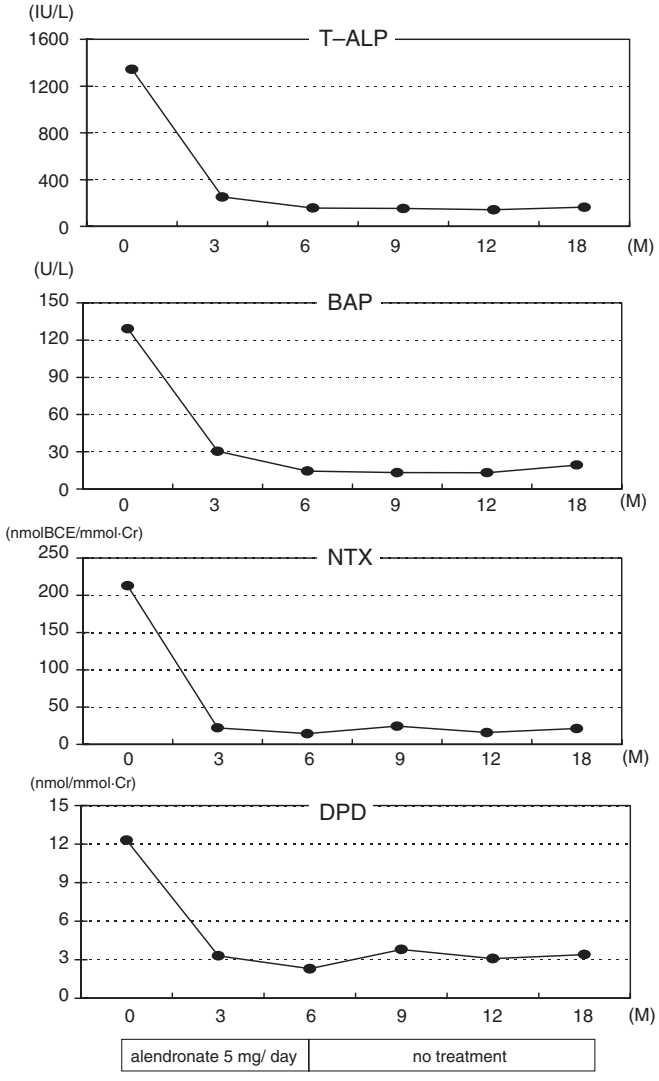

Fig. 1. Changes in bone turnover markers in case 1. *T-ALP*, total alkaline phosphatase; *BAP*, bone-specific alkaline phosphatase; *NTX*, N-terminal telopeptide of type I collagen; *DPD*, deoxypyridinoline; *BCE*, bone collagen equivalent; *Cr*, creatinine; *M*, months

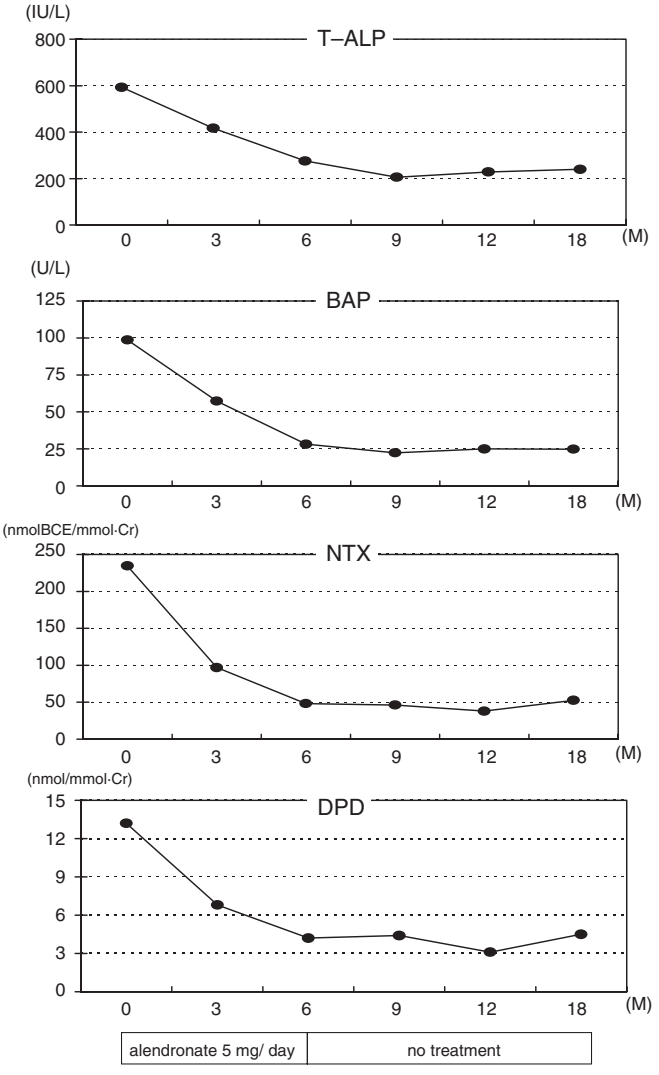

Fig. 2. Changes in bone turnover markers in case 2

high levels of T-ALP (593 IU/l), BAP (98.6 U/l; cutoff range in Japanese women, ≤75.7 U/l), urinary NTX (234.6 nmolBCE/mmol·Cr; cutoff range in Japanese women, ≤89.0 nmolBCE/mmol·Cr), and DPD (13.2 nmol/mmol·Cr; cutoff range in Japanese women: ≤13.1 nmol/mmol·Cr; Fig. 2). The diagnosis of Paget's disease was made on the basis of the results of radiography, bone scintigraphy, and laboratory examinations. Open biopsy was done to confirm the diagnosis. Histology showed a mosaic structure of resorption and formation, and there was no evidence of a malignant neoplasm or other bone disease.

The patient was treated with alendronate, at 5 mg per day, orally, and alphacalcidol (1.0 μg/day), and daily calcium intake was set at 1000 mg. Nonsteroidal anti-inflammatory drugs had not been taken. The low back pain and excessive warmth over bone disappeared within 3 months. Six months after the start of alendronate treatment, bone turnover had reached the normal range (T-ALP, 276 IU/l; BAP, 28.2 U/l; NTX, 48.2 nmolBCE/mmol·Cr; DPD, 4.2 nmol/mmol; Fig. 2). Radiography and computerized tomography at 6 months did not show any changes. The biochemical remissions persisted for 1 year after the discontinuance of treatment.

Discussion

We have reported two cases of Paget's disease in Japanese patients treated with a low dose of alendronate (5 mg per day orally) for 6 months. In the protocol for the treatment of Paget's disease, the dose of alendronate is 40 mg daily [5], whereas the dose for the treatment of osteoporosis is 10 mg daily [6,7]. Although alendronate is not available for the treatment of Paget's disease in Japan, etidronate is available for this purpose. The reasons that we used a low dose of alendronate, rather than etidronate for the two patients

described here are as follows. First, the dose of etidronate that most effectively reduces increased bone resorption can also impair mineralization [1]. Second, etidronate is contraindicated in the presence of lytic changes in a weight-bearing bone [1]. Third, in a single comparative study, in which alendronate was compared with etidronate [2], the alendronate-treated group had significantly greater decreases in both T-ALP (79% vs 44%) and DPD (75% vs 51%) than the etidronate-treated group ($P < 0.001$ for both markers). In addition, normalization of T-ALP was much more frequent in alendronate-treated patients (63.4% vs 17.0%; $P < 0.001$) [2]. Fourth, the suitability of alendronate for Japanese seems to be different from that for Caucasians, because the dose of alendronate for the treatment of osteoporosis in Japanese (5 mg/day) is half that used for the treatment of osteoporosis in Caucasians (10 mg/day). The difference in dosage between Caucasians and Japanese may be explained by an ethnic difference in pharmacokinetics [8]. This suggests that a low dose of alendronate may be effective in Japanese patients with Paget's disease. Finally, the degree of elevation of bone metabolic markers offers an approximation of the extent or severity of the abnormal bone turnover, with higher levels reflecting a more active, ongoing localized metabolic process [1]. For example, patients with the highest T-ALP elevations (e.g., > ten times the upper limit of normal) have involvement of the skull as at least one site of the disorder. On the other hand, lower values (e.g., < three times the upper limit of normal) may reflect a lesser extent of involvement [1]. In both our patients, the values for T-ALP, BAP, NTX, and DPD were approximately 1.0–3.6 times the upper limits of normal, indicating that the disease was of lesser extent.

In both of our patients, alphacalcidol (1.0 μg/day) and a daily calcium intake of 1000 mg were also given, to prevent a secondary increase in PTH. The administration of alphacalcidol and a calcium supplement may not be necessary with a low dose of alendronate; however, Siris et al. [9] suggested that pagetic osteoclasts were more sensitive to PTH than were osteoclasts in unaffected parts of the skeleton. Moreover, the acute inhibition of osteoclasts in conditions of high bone turnover leads to a rapid fall in serum calcium levels, followed by an increase in the level of PTH [10,11], and this is an important concept to explore in optimizing bisphosphonate therapy, not only for Paget's disease but probably for osteoporosis as well, in which bisphosphonate therapy also promotes a secondary parathyroid response [12].

It has been reported that suppression of serum ALP to within the normal range is a prerequisite for obtaining long-term remission in Paget's disease of bone [13]. Retreatment is recommended when indices increase above the upper limits of normal ranges or when they increase by 25% above the previous nadir [14]. Both patients described here showed no increase in bone turnover for 1 year after the discontinuance of treatment. In addition, the therapeutic efficacy and prognosis of the low dose of alendronate was not different from these features with a high dose of alendronate [1]. Khan et al. [15] described four treatment regimens of alendronate in patients with Paget's disease (two groups were treated with either 40 or 80 mg/day for 3 months, followed by placebo for a further 3 months; the other two groups were treated with either 40 or 80 mg/day for 6 months) [15]. Alendronate induced a marked suppression of the urinary excretion of hydroxyproline and serum T-ALP in all treatment groups. Although there has been no report that a low dose of alendronate is effective for the patient with a lesser extent of involvement or lower values for bone metabolic markers, our results clearly indicate that a low dose of alendronate is effective for treating Japanese patients with Paget's disease that affects of half of the pelvis. We therefore recommend that treatment for Japanese patients with Paget's disease, especially those with disease affecting only one site, should start with a low dose of alendronate.

The guidelines for the management of Paget's disease in the United Kingdom recommend that the first-line management of Paget's disease should use bisphosphonates, such as oral tiludronate, oral risedronate, or intravenous pamidronate [5]. Etidronate is not recommended for the treatment of Paget's disease. Paget's disease is rare in Japan; however, guidelines for Japanese patients should be developed, and more effective bisphosphonates for this purpose should be licensed in future.

References

1. Siris ES, Roodman GD (2003) Paget's disease of bone. In: Favus MJ (ed) Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. American Society for Bone and Mineral Research, Washington DC, pp 495–506
2. Siris E, Weinstein RS, Altman R, Conte JM, Favus M, Lombardi A, Lyles K, McIlwain H, Murphy WA Jr, Reda C, Rude R, Seton M, Tiegs R, Thompson D, Tucci JR, Yates AJ, Zimering M (1996) Comparative study of alendronate vs etidronate for the treatment of Paget's disease of bone. J Clin Endocrinal Metab 81: 961–967
3. Reid IR, Nicholson GC, Weinstein RS, Hosking DJ, Cundy T, Kotowicz MA, Murphy WA Jr, Yeap S, Dufresne S, Lombardi A, Musliner TA, Thompson DE, Yates AJ (1996) Biochemical and radiologic improvement in Paget's disease of bone treated with alendronate: a randomized, placebo-controlled trial. Am J Med 171: 341–348
4. Lombardi A (1999) Treatment of Paget's disease of bone with alendronate. Bone 24: 59S–61S
5. Selby PL, Davie MWJ, Ralston SH, Stone MD (2002) Guidelines on the management of Paget's disease of bone. Bone 31: 366–373
6. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE (1996) Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 348: 1535–1541
7. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ (1998) Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the fracture intervention trial. JAMA 280: 2077–2082
8. Kushida K, Shiraki M, Nakamura T, Kishimoto H, Morii H, Yamamoto K, Kaneda K, Fukunaga M, Inoue T, Nakashima M, Orimo H (2004) Alendronate reduced vertebral fracture risk in postmenopausal Japanese women with osteoporosis: a 3-year follow-up study. J Bone Miner Metab 22: 462–468
9. Siris ES, Canfield RE, Jacobs TP, Stoddart KE, Spector PJ (1981) Clinical and biochemical effects of EHDP in Paget's disease of

bone: pattern of response to initial treatment and to long therapy. Metab Bone Dis Relat Res 3: 301–308
10. Delmas PD, Chapuy MC, Vignon E, Charhon S, Briancon D, Alexandre C, Edouard C, Meunier PJ (1982) Long term effects of dichloromethylene diphosphonate in Paget's disease of bone. J Clin Endocrinal Metab 54: 837–844
11. Harris ST, Neer RM, Segre GV, Petkau AJ, Tully GL 3rd, Daly M, Potts Jr JT (1982) Secondary hyperparathyroidism associated with dichloromethane diphosphonate treatment of Paget's disease. J Clin Endocrinal Metab 55: 1100–1107
12. Adami S, Zamberlan N, Mian M, Dorizzi R, Rossini M, Braga B, Gatti D, Bertoldo F, Locascio V (1994) Duration of the effects of intravenous alendronate in postmenopausal women and in patients with primary hyperparathyroidism and Paget's disease of bone. Bone Miner 25: 75–82
13. Eekhoff MEMW, Zwinderman AH, Haverkort DMAD, Cremers SCLM, Hamdy NAT, Papapoulou SE (2003) Determinants of induction and duration of remission of Paget's disease of bone after bisphosphonate (olpadronate) therapy. Bone 33: 831–838
14. Siris ES (1999) Goals of treatment for Paget's disease of bone. J Bone Miner Res 14 (Suppl 2): 49–52
15. Khan SA, Vasikaran S, McCloskey EV, Benéton MNC, Rogers S, Coulton L, Orgee J, Coombes G, Kanis JA (1997) Alendronate in the treatment of Paget's disease of bone. Bone 20: 263–271