Clinical and Experimental Rheumatology 2007; 25: 464-466.

Persistent effect of zoledronic acid in Paget's disease

K. Tziomalos, M. Florentin, N. Krikis, V. Perifanis, A. Karagiannis, F. Harsoulis

2nd Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, Hippokration Hospital, Thessaloniki, Greece.

Konstantinos Tziomalos, MD; Matilda Florentin, MD; Napoleon Krikis, MD; Vassilios Perifanis, MD; Asterios Karagiannis, MD, Associate Professor in Internal Medicine; Faidon Harsoulis, MD, Professor in Endocrinology.

Please address correspondence and reprint requests to: Dr. Konstantinos Tziomalos, 63 Solonos Street, Thessaloniki, 54248 Greece.
E-mail address: ktziomalos@yahoo.com

Received on April 5, 2006; accepted in revised form on September28, 2006.

Key words: Paget's bone disease, zoledronic acid, bisphosphonates, alkaline phosphatase, sustained remission.

Competing interests: none declared.

ABSTRACT

Paget's bone disease is a disorder in which bone regions with high turnover are replaced by new, vascular, but disorganized and immature bone with excessive fibrosis, high tendency of deformity and diminished mechanical resistance. Treatment aims at the suppression of osteoclast activity and is achieved with bisphosphonates, which represent the treatment of choice for Paget's disease. Zoledronic acid, a relatively new member of this class, normalizes alkaline phosphatase in the majority of patients and has a favorable safety profile. We report the case of an asymptomatic patient who was diagnosed with Paget's disease based on typical biochemical, radiological and histological findings and was treated with a single intravenous infusion of 4 mg of zoledronic acid. No side effects were observed. Alkaline phosphatase levels normalized within four months. At the last follow up examination, three years after treatment, the patient remains asymptomatic, without significant changes in radiology imaging, and alkaline phosphatase levels are still within the normal range. In conclusion, zoledronic acid, apart from being safe and effective in Paget's disease, also appears to be able to achieve significantly prolonged remissions.

Introduction

Paget's bone disease is a disorder in which bone regions with high turnover are replaced by new, vascular, but disorganized and immature bone with excessive fibrosis, high tendency of deformity and diminished mechanical resistance (1, 2). It is quite frequent in Europe being present in 3% of the population above 55 years old (1-3). Its etiology remains unknown; genetic predisposition and environmental factors may contribute to its pathogenesis (2-5). Most patients are asymptomatic and the disease is usually discovered incidentally due to elevated biochemical indices of bone turnover or due to characteristic radiological bone lesions. When symptomatic, the primary manifestations include bone pain, skeletal deformities, fractures and osteoarthritis. Malignant transformation to osteosarcoma, fibrosarcoma or chondrosarcoma develops in less than 1% of patients (1, 6).

Treatment aims at the suppression of osteoclast activity and is achieved with bisphosphonates, which represent the treatment of choice for Paget's disease (1, 7). Zoledronic acid is a novel, more potent compound, which effectively inhibits osteoclast activity without inhibiting osteoid mineralization (8-10). The sustained effect of zoledronic acid in a patient with Paget's disease is reported.

Case report

A 60-year-old man presented in the Emergency Department of our clinic due to left kidney colic. He had suffered acute myocardial infarction 11 years before and, shortly afterwards, a coronary artery bypass grafting (CABG) was performed. His treatment included metoprolol, acetylsalicylic acid and atorvastatin. He also reported several episodes of renal colic due to nephrolithiasis.

Physical examination was unremarkable. On admission, laboratory examination was significant for elevated alkaline phosphatase (ALP) levels, 321IU/L (normal range, 30-125 IU/L). The pelvis-hip-lumbar spine-femur radiography revealed the presence of diffuse osteoblastic lesions, small disseminated lytic regions and trabecular thickness. In addition, cortical bone thickness, enlargement of the diaphysis, bowing deformities and small horizontal pseudofractures on the upper third of the left femur were observed (Fig. 1).

Histological examination of a bone specimen obtained from the right ilium showed loss of architectural structure of the osseous trabeculae, mosaic appearance of the osseous lamella, increased osteoclast activity and fibrosis of the marrow spaces were confirmed (Fig. 2).

Typical biochemical, radiological and histological findings established the diagnosis of Paget's disease. The patient was treated with a single intravenous infusion of 4 mg of zoledronic acid given over a fifteen-minute period. No side effects were observed. Alkaline

Fig. 1. Pelvis-hip-lumbar spine-femur radiography showing diffuse osteoblastic lesions, small disseminated lytic regions and trabecular thickness.

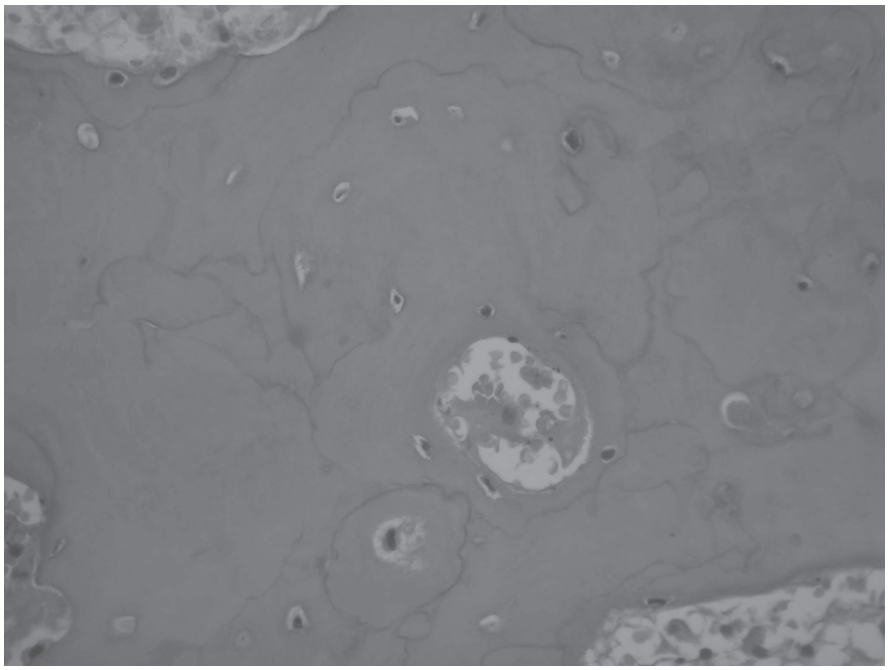

Fig. 2. Histological examination of a bone specimen obtained from the right ilium showing mosaic appearance of the osseous lamella (Haematoxylin and eosin, x 400).

phosphatase levels normalized within four months (60 IU/L). At the last follow up examination, three years after treatment, the patient remains asymptomatic, without significant changes in radiology imaging, and alkaline phosphatase levels are still within the normal range.

Discussion

Paget's disease is usually asymptomatic at diagnosis. Pain is not a reliable indicator of the extent of the disease, since more than 70% of the lesions is asymptomatic (11). Vertebrae, long bones and skull are the most commonly involved sites. The most characteristic radiological finding is localized bone expansion, which is absent in all other diseases that cause osteosclerosis. Cortical bone thickness and lytic lesions are observed as well. The biopsy findings are pathognomonic of the disease. "Paved" or "mosaic" appearance of the osseous tissue, irregular collagen disposition, hypervascularity and an elevated number of osteoblasts and osteoclasts with multiple nuclei are present (1).

Evaluation of disease activity and its response to treatment is based on the determination of alkaline phosphatase, which reflects osteoblast activity (12). Other markers of bone turnover, such as osteocalcin and urinary hydroxyproline, do not appear to be more sensitive than alkaline phosphatase (3, 13). However, recent studies have shown that serum cross-linked C-telopeptides of type I collagen is a sensitive marker of bone resorption in the management of bisphosphonate therapy in Paget's disease (14).

The primary disorder in Paget's disease is increased bone resorption. Bisphosphonates increase osteoclasts' apoptosis, directly suppress their activity and inhibit the proliferation of osteoclasts' precursors (15). Zoledronic acid is a particularly attractive bisphosphonate, because it increases bone density and restores bone architecture, in contrast to older members of this class, which caused disorders in the osteoid mineralization (5, 10). These favorable characteristics are attributed to the zoledronic acid-induced stimulation of proliferation, differentiation and osteosynthetic capacity of osteoblasts (15).

Administration of zoledronic acid has recently been shown to normalize alkaline phosphatase in 88.6% of patients with Paget's disease, whereas other bisphosphonates induced complete remissions in only 50-60% of the cases (7, 10, 16). In addition, the same study demonstrated that after a median follow-up time of 190 days, only 1 out of 113 patients who received a single infusion of 5 mg of zoledronic acid had a loss of therapeutic response, in comparison to 21 out of 82 patients treated with risedronate (30 mg per day for 60 days, orally) (16). Our patient received a single dose of zoledronic acid intra-

venously and, three years after treatment, alkaline phosphatase levels are within normal levels, something that clearly shows the persistence of the effect of zoledronic acid. In contrast, older bisphosphonates must be administered for long periods of time, at least for six months, in order to achieve and maintain a response.

Another major disadvantage of currently used bisphosphonates in Paget's disease is that they are administered orally. This is associated with poor absorption from the gastrointestinal tract and the frequent development of side effects, particularly gastrointestinal distress and erosive esophagitis (1). In contrast, zoledronic acid is given intravenously, resulting in superior pharmacokinetic characteristics and has a favorable safety profile. Moreover, it is safer and more effective than pamidronate, which is the only other bisphosphonate given intravenously for Paget's disease (9).

The safety and efficacy of bisphosphonates extended the indications of treatment to asymptomatic patients. Thus, the risk of developing fractures or neurological disorders due to involvement of the basis of the skull, the vertebral column or the long bones of lower extremities make bisphosphonate administration imperative (5). Additional indications for treatment are young patients and highly active disease. Nevertheless, it has still not been established if decreasing the rate of bone turnover also decreases complications. Thus, treatment indications remain empirical and should be individualized (6).

Patient follow up is based on alkaline phosphatase determination every 4-6 months and treatment should be repeated when alkaline phosphatase levels rise above the upper limit of normal (10). Radiology imaging of the involved bones should also be repeated, particularly if the skull or the bones of the lower extremities are involved, since bisphosphonate administration might restore bone architecture (1). In conclusion, zoledronic acid appears to be safe and effective in Paget's disease, and most importantly, able to achieve significantly prolonged remissions.

References

1. DELMAS PD, MEUNIER PJ: The management of Paget's disease of bone. *N Engl J Med* 1997; 336: 558-66.
2. NOOR M, SHOBACK D: Paget's disease of bone: diagnosis and treatment update. *Curr Rheumatol Rep* 2000; 2: 67-73.
3. FRASER WD: Paget's disease of bone. *Curr Opin Rheumatol* 1997; 9: 347-54.
4. REDDY SV, KURIHARA N, MENAA C, ROODMAN GD: Paget's disease of bone: a disease of the osteoclast. *Rev Endocr Metab Disord* 2001; 2: 195-201.
5. SIRIS ES: Paget's disease of bone. *J Bone Miner Res* 1998; 13: 1061-5.
6. TIEGS RD: Paget's disease of bone: indications for treatment and goals of therapy. *Clin Ther* 1997; 19: 1309-29.
7. GATTI D, ADAMI S: New bisphosphonates in the treatment of bone diseases. *Drugs Aging* 1999; 15: 285-96.
8. OADES GM, SENARATNE SG, CLARKE IA, KIRBY RS, COLSTON KW: Nitrogen containing bisphosphonates induce apoptosis and inhibit the mevalonate pathway, impairing Ras membrane localization in prostate cancer cells. *J Urol* 2003; 170: 246-52.
9. WIDLER L, JAEGGI KA, GLATT M *et al*.: Highly potent geminal bisphosphonates. From pamidronate disodium (Aredia) to zoledronic acid (Zometa). *J Med Chem* 2002; 45: 3721-38.
10. SIRIS ES: Goals of treatment for Paget's disease of bone. *J Bone Miner Res* 1999; 14 Suppl. 2: 49-52.
11. MEUNIER PJ, SALSON C, MATHIEU L *et al*.: Skeletal distribution and biochemical parameters of Paget's disease. *Clin Orthop Relat Res* 1987; 217: 37-44.
12. RANDALL AG, KENT GN, GARCIA-WEBB P *et al*.: Comparison of biochemical markers of bone turnover in Paget disease treated with pamidronate and a proposed model for the relationships between measurements of the different forms of pyridinoline cross-links. *J Bone Miner Res* 1996; 11: 1176-84.
13. WOITGE HW, OBERWITTLER H, HEICHEL S, GRAUER A, ZIEGLER R, SEIBEL MJ: Short- and long-term effects of ibandronate treatment on bone turnover in Paget disease of bone. *Clin Chem* 2000; 46: 684-90.
14. CACACE E, RUGGIERO V, MATULLI C, URAS L, PERPIGNANO G: Markers of bone resorption in bisphosphonate therapy of Paget's disease. *Clin Exp Rheumatol* 2004; 22: 502.
15. REINHOLZ GG, GETZ B, PEDERSON L *et al*.: Bisphosphonates directly regulate cell proliferation, differentiation, and gene expression in human osteoblasts. *Cancer Res* 2000; 60: 6001-7.
16. REID IR, MILLER P, LYLES K *et al*.: Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *N Engl J Med* 2005; 353: 898-908.