J Orthopaed Traumatol (2006) 7:192–194
DOI 10.1007/s10195-006-0147-4

BRIEF COMMUNICATION

Usefulness of osteoprotegerin in assessing responses to neridronate treatment in Paget's disease of bone

F.M. Ulivieri
L.P. Piodi
G. Marotta
D. Marchelli
C. Corradini
L. Parravicini
C. Verdoia
P. Gerundini

Received: 2 February 2006
Accepted: 2 October 2006
Published online: 18 December 2006

F.M. Ulivieri (✉) • G. Marotta
D. Marchelli • P. Gerundini
Department of Nuclear Medicine
Ospedale Maggiore
Fondazione IRCCS
Padiglione Granelli
Via F. Sforza 35, Milan, Italy
E-mail: ulivieri@policlinico.mi.it

L.P. Piodi
Department of Gastroenterology
Ospedale Maggiore
Fondazione IRCCS
Milan, Italy

L. Parravicini • C. Corradini • C. Verdoia
Department of Orthopaedics and Traumatology
G. Pini Hospital
University of Milan
Milan, Italy

Abstract Osteoprotegerin (OPG) is a protein that inhibits of osteoclastogenesis. The aim this study was to evaluate the response of serum OPG levels to neridronate treatment in patients with Paget's disease of bone resistant to previous therapy. Nine patients (4 men) affected by active Paget's disease of bone (6 polyostotic, 3 monostotic) not responsive to clodronate were studied. Serum OPG, osteocalcin, total and bone isoenzyme of alkaline phosphatase (AP and BAP, respectively), and urinary deoxypyridinoline (DPD) were measured before and 5 months after neridronate treatment (100 mg/day, i.v. for two days). A scintigraphic activity index (SAI) was also calculated before treatment. Mean baseline OPG levels were within normal values and were not significantly different 5 months after neridronate treatment. In contrast, there were significant reductions in AP (41.9%, $p<0.02$) and BAP (38.8%, $p<0.04$). Serum OPG levels correlated with DPD (r=0.925) and SAI (r=0.689). Although OPG is an important regulator of bone metabolism, in our series of already treated patients it was not a sensitive marker for diagnosing Paget's disease and for monitoring the response to pharmacological treatment, whereas AP and BAP confirmed their clinical usefulness. This preliminary study requires confirmation by a study with a larger population.

Key words Bone metabolism • Neridronate • Osteoprotegerin • Paget's disease of bone

Introduction

Paget's disease of bone is a local disorder of bone remodeling characterized by an excessive increase in the metabolic activity of bone. An acceleration of osteoclast-mediated bone resorption, followed by an increase in osteoblastic activity, leads to replacement of normal bone by an abnormal and weakened bone structure that is prone to pain, deformity and fracture [1]. The present first-choice treatment for Paget's disease of bone are bisphosphonates, whose main function is to decrease bone resorption by inhibiting osteoclast activity [2]. A recent bisphosphonate used for this purpose is neridronate (6-amino-1-hydroxyhexilidene-1,1-bisphosphonate monosodium), a third-generation aminobisphosphonate, which is well tolerated even at high doses [3].

To monitor the effectiveness of these drugs in follow-up, usual biochemical parameters of bone formation and resorption are widely assessed. Recently, some new members of the tumor necrosis factor receptor family have been identified as regulators of osteoclastogenesis and

bone resorption: osteoprotegerin (OPG) and its ligand (RANKL), the receptor activator of nuclear factor-Kappa B ligand. OPG binds to RANKL, an essential cytokine required for osteoclastogenesis, and inhibits osteoclast differentiation, suppresses activation of mature osteoclasts, and drives them into apoptosis [4, 5].

Recently, Alvarez et al. [6] described high serum levels of OPG in patients with Paget's disease of bone. These levels decreased after treatment with tiludronate, but there was no correlation between serum OPG levels and markers of bone turnover or scintigraphic indices [6]. So far, this is the only report concerning OPG and treatment of Paget's disease with bisphosphonate. Therefore, the aim of this preliminary study was to evaluate the usefulness of monitoring serum OPG levels to assess the response to neridronate therapy in already treated patients with Paget's disease of bone.

Patients and methods

Nine patients affected by Paget's disease of bone (4 men and 5 women; age range, 59-80 years; mean±SD, 71±8.7) were included in the study. The diagnosis of Paget's disease was made by radiography and bone scintigraphy. Three patients had monostotic and 6 had polyostotic disease. Liver and renal function tests were normal in all patients.

The patients had been previously treated with clodronate (300 mg/day, i.v. for five days) for a mean of 2.7 courses of therapy (range, 1-5), and were all judged to be non-responders. Lack of response to this therapy was defined as a reduction in serum alkaline phosphatase (AP) five months after treatment by less than 50% of the pre-treatment value and still remaining above the upper limit of the normal range. For this reason, patients were switched to a single course of neridronate (100 mg/day, i.v. for two days). The criteria to classify non-responders were in accordance with previous protocols [3, 7].

Laboratory assessment was carried out before and five months after neridronate treatment. A blood sample and a 2-hour morning urine sample were collected from each subject after an overnight fast. Serum and urine were stored at -20° C until analysis. We measured: serum OPG (Bio Vendor, Brno, Czech Republic); serum AP (Roche; Basel, CH); serum osteocalcin; serum bone isoenzyme of alkaline phosphatase (BAP); and urinary deoxypyridinoline/creatinine excretion (DPD) (Quidel; San Diego, CA, USA). The intraassay and interassay coefficients of variation (CV) for each marker were, respectively: OPG, 5.0% and 4.7%; AP, 2.0% and 3.0%; osteocalcin, 7.8% and 7.0%; BAP, 5.0% and 5.9%; and DPD, 6.1% and 4.2%.

The upper limits of normal values were those from our normal laboratory population: OPG (mean±SD), 14.59±3.88 U/L; AP, 77.95±20.24 U/L; osteocalcin, 6.30±2.45 ng/ml; BAP, 25.24±8.11 U/L; DPD, 4.40±1.20 nmol/mmol.

Before neridronate treatment, quantitative bone scintigraphy was performed 2 hours after an intravenous injection of 740 MBq (20 mCi) of ^{99m}Tc-labeled hydroxymethylene bisphosphonate. The scintigraphic disease activity index (SAI) of Pons et al. [8] was calculated.

All subjects gave written informed consent to the study, and the principles of the Declaration of Helsinki were followed.

Student's *t* test for paired and unpaired data, and Pearson's correlation test were used for statistical analysis.

Results

We measured the responses of bone metabolism markers to neridronate treatment in 9 patients with Paget's disease of bone unresponsive to clodronate. Five months after neridronate treatment, we observed significant reductions in serum levels of AP and BAP (41.9% and 38.8%, respectively) compared to pretreatment values (Table 1). Serum levels of OPG, before and after treatment, were within normal levels, and the reduction after treatment (5.1%) was not statistically significant. There were no significant changes in osteocalcin or DPD levels.

SAI values ranged from 13 252 to 11 4028 (mean±SD, 55367±39009) and correlated with OPG levels (Pearson's r=0.689; p=0.040). Moreover, we observed significant correlations (p=0.001) between OPG and DPD (r=0.925) and between BAP and AP (r=0.886).

Table 1 Serum osteoprotegerin (OPG) and markers of bone turnover in 9 patients with Paget's disease of bone, before and 5 months after neridronate treatment

	Before treatment	After treatment
OPG (U/L)	11.01 (3.82)	10.44 (3.76)
AP (U/L)	1081 (297)	628 (374)*
BAP (U/L)	200.63 (62.46)	122.86 (90.75)**
Osteocalcin (ng/ml)	11.64 (5.81)	11.85 (3.06)
DPD (nmol DPD/mmol creatinine)	15.41 (9.78)	10.33 (5.13)

*p<0.02; **p<0.04 vs. before treatment, Student's *t* test for paired data

Discussion

Our data do not confirm previous observations [6], because serum levels of OPG in these patients were in the range of normal values. However, one can take into account that none of the patients in the work of Alvarez et al. [6] had been treated with bisphosphonates during the previous two years nor with calcitonin during the previous year. In our series, no variations of OPG were observed after neridronate therapy. Also osteocalcin and DPD did not present significant reductions after treatment; their values remained slightly above the upper limits of normal, both before and after therapy. On the contrary, as expected in Paget's disease of bone, AP and BAP underwent statistically significant decreases after neridronate administration, even if they did not reach the normal values. Reduction in serum AP and BAP after bisphosphonate treatment is still widely used for monitoring the efficacy of therapy in patients with Paget's disease of bone [9].

One explanation for the absence of a significant variation in OPG, osteocalcin and DPD after therapy could be the limited statistical power of the study due to the small number of cases. Otherwise, another hypothesis is the low bone turnover in these patients, who had been previously repeatedly treated with clodronate, a non-selective first-generation bisphosphonate. Another consideration is that OPG determinations were carried out at basal time and after 5 months. Therefor, we cannot exclude a possible temporary decrease of serum OPG before the fifth month after neridronate administration. Nevertheless, the positive correlation between OPG and SAI may indicate that OPG is related to disease activity, and the positive correlation with DPD can be explained by a compensatory inhibitory mechanism of osteoclastic hyperactivity carried out by OPG.

In conclusion, our preliminary data suggest that OPG is not useful for assessing activity and response to re-treatment in Paget's disease of bone, even if it is an important regulator of bone metabolism. On the contrary, the study confirms the usefulness of AP and its bone isoenzyme also in those patients with low bone remodeling due to previous courses of bisphosphonate treatment. The results of this preliminary study should be confirmed in studies with a larger number of cases.

References

1. Siris ES (1998) Paget's disease of bone. J Bone Miner Res 13:1061–1065
2. Fleisch H (1993) Bisphosphonates in osteoporosis: an introduction. Osteoporos Int 3[Suppl 1]:S3–S5
3. Adami S, Bevilacqua M, Broggini M, Filipponi P, Ortolani S, Palummeri E et al (2002) Short-term intravenous therapy with neridronate in Paget's disease. Clin Exp Rheumatol 20:55–58
4. Lacey DL, Timms E, Tan H-L, Kelley MJ, Dunstan CR, Burgess T et al (1998) Osteoprotegerin (OPG) ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 93:165–176
5. Aubin JE, Bonnelye E (2000) Osteoprotegerin and its ligand: a new paradigm for regulation of osteoclastogenesis and bone resorption. Osteoporos Int 11:905–913
6. Alvarez L, Peris P, Guañabens N, Vidal S, Ros I, Pons F et al (2003) Serum osteoprotegerin and its ligand in Paget's disease of bone. Arthritis Rheum 48:824–828
7. Filipponi P, Cristallini S, Policani G, Casciari C, Gregorio F (1998) Paget's disease of bone: benefits of neridronate as a first treatment and in cases of relapse after clodronate. Bone 23:543–548
8. Pons F, Alvarez L, Peris P, Guañabens N, Vidal-Sicart S, Monegal A et al (1999) Quantitative evaluation of bone scintigraphy in the assessment of Paget's disease activity. Nucl Med Commun 20:525–528
9. Reid IR, Davidson JS, Wattie D, Wu F, Lucas J, Gamble GD et al (2004) Comparative responses of bone turnover markers to bisphosphonate therapy in Paget's disease of bone. Bone 35:224–223