Effects of monthly intramuscular neridronate in rheumatic patients in chronic treatment with low-dose glucocorticoids

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Abstract

Objectives

To assess the effects of intramuscular (im) neridronate (NE) on lumbar and femoral neck BMD and on markers of bone turnover in rheumatic patients under chronic low-dose glucocorticoids (GC) therapy.

Methods

Sixty-nine osteopoenic and osteoporotic patients, affected by rheumatic diseases and gastric or esophageal conditions which contraindicated treatment with oral bisphosphonates (BPs), were randomly assigned to: Group A (23 patients) administered with daily calcium 1 g and vitamin D 800 UI; Group B (46 patients) receiving daily calcium 1 g, vitamin D 800 UI and im NE 25 mg monthly.

Results

After 12 months of therapy (M12) lumbar BMD was reduced of 2.97% in Group A, and improved of 3.34% ($p=0.001$) in Group B; at M12, femoral neck BMD was reduced of 2.40% in Group A and improved of 1.78% in Group B ($p=0.010$). After 6 (M6) and 12 months of therapy, the bone resorption markers were significantly reduced in Group B: OHPr-41.64% at M6 ($p<0.001$) and -37.91% at M12 ($p<0.001$); DPD-33.4% at M6 ($p<0.001$) and -33.18% ($p<0.001$) at M12: NTX -57.08% ($p<0.001$) at M6 and -55.95% ($p<0.001$) at M12; OC-11.62% ($p=0.05$) at M6 and -12.62% at M12 ($p=0.06$); B-ALP -13.95 % at M6 ($p=0.04$) and -0.85% at M12 (NS).

Conclusions

A twelve-month intramuscular NE treatment in rheumatic patients under GCs therapy improves lumbar and femoral BMD and mainly reduces the markers of bone resorption.

Key words

Neridronate, bisphophonates, bone markers, glucocorticoid induced osteoporosis, rheumatic diseases.

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Abbreviations:

BP:	bisphosphonates
NE:	neridronate
DMARD:	disease modifying anti-rheumatic drug
M0:	baseline
M6:	at 6 months
M12:	at 12 months
GIO:	glucocorticoid-induced osteoporosis
CRP:	C-reactive protein
ESR:	erythrocyte sedimentation rate
B-ALP:	bone-specific alkaline phosphatase
PTH:	intact parathyroid hormone
OC:	osteocalcin
DPD:	urine deoxypyridinoline
NTX:	urinary cross-linked N-telopeptides of bone type I collagen
OHPr:	hydroxyprolinuria
BMD:	bone mineral density
CV:	coefficient of variation

Competing interests: none declared.

Introduction

Glucocorticoid-induced osteoporosis (GIO) and osteoporosis-related fractures are the most common and serious side-effects for rheumatic patients on long-term therapy with glucocorticoids (GCs) (1).

Oral bisphosphonates (BPs) – alendronate, risedronate, ibandronate – have been successfully used for the treatment of osteoporosis, including GIO, to prevent bone fractures (2, 3). However, there are two main problems in the use of oral BPs: the first major obstacle is represented by the frequent lack of compliance. The reasons behind the poor observance of the treatment are the following:

- oral BP can cause gastrointestinal adverse effects, especially esophagitis (4, 5);
- a large amount of water is needed when taking the tablets;
- 30/60-minutes upright posture is required after the administration of BP;
- the co-administration of any other drug, food or beverage is forbidden for at least half an hour;
- the compliance falls as the number of daily drugs increases: this is a very common situation in elderly patients, including those treated with GCs and DMARDs for rheumatic diseases in which BPs are recommended as first-line drugs in addition to calcium and vitamin D (6-12).

Secondly, gastrointestinal absorption of oral BP is very low (<1%), thus causing low bioavailability of these drugs.

For these two main reasons, new intravenous (iv) formulations of BPs have been developed allowing very long intervals of administration, avoiding gastrointestinal side-effects and improving compliance (7, 13). Moreover, in Italy, intramuscular (im) clodronate administered weekly was the most used BP for the treatment of osteoporosis till 2006: this suggests that Italian osteoporotic patients have a good adherence to intramuscular treatments.

Neridronate (NE), 6-amino-1-hydroxyhexylidene-1,1-bisphosphonate, is an amino-bisphosphonate available only in ampoules of 25 or 100 mg for im and iv injections. NE is currently registered only in Italy for the treatment of osteogenesis imperfecta and Paget's disease (14-18). However, several recent papers showed that NE can also be effective in treating post-menopausal osteoporosis, and that the dose of 25 mg/monthly is the most effective (19-22). Moreover, NE is reported to be effective also for osteoporosis in hypogonadic men (23), transient osteoporosis of the hip (24), avascular bone necrosis (25), multiple myeloma (26) and also that it can significantly reduce markers of bone turnover in patients treated with GCs (27).

In rheumatology, low-dose GCs, normally in association with DMARDs are often essential in the treatment of chronic inflammatory arthropathies, but the diagnostic threshold in GIO, using BMD, is different from the established guidelines for postmenopausal osteoporosis. In fact, if GC users, patients with similar BMD levels have a higher risk of fractures than non-users (28). For this reason the Royal College of Physicians of London has proposed to take into account a T-score of -1.5 DS for therapeutic intervention, while the American College of Rheumatology has developed recommendations to prevent and to treat glucocorticoid-induced osteoporosis (29, 30).

In this study, we report the results of a randomized controlled trial on the effects of NE administered on a monthly basis to prevent GIO in rheumatic patients.

The primary aim of this study was to verify the efficacy of a 12-month treatment with intramuscular NE (25 mg/monthly) on the lumbar and femoral BMD in rheumatic patients under chronic treatment with low-dose GC. Secondary objective was to evaluate at Month 12 the bone metabolic effects of NE.

Material and methods

Patients

Centres participating in the study were the Rheumatology Unit of the Nuovo Ospedale San Giovanni di Dio in Florence, the Rheumatology Unit of the University of Verona and the Rheumatology and Rehabilitation Unit of the Salvatore Maugeri Foundation in Castel Goffredo, Mantova.

The protocol was approved by an independent Ethics Committee (Comitato Etico della Fondazione Salvatore

Maugeri di Pavia). All patients gave their written informed consent to the treatment with im NE (Nerixia®, Abiogen Pharma, Pisa, Italy), obtained according to the Declaration of Helsinki and subsequent legal documents.

Inclusion criteria: males and females aged between 18 and 85, affected by rheumatic diseases and in treatment with stabilized low-dose GC (methylprednisolone ≤8 mg daily) for more than 4 months; intrarticular injections of corticosteroids were not allowed; spine or femoral-neck BMD T-score at least -1.5 DS below peak; contraindications for treatment with oral BP because of gastric or oesophageal diseases or because of previous intolerance (in this case BPs were administered for less than one month and stopped at least 6 months before the enrolment).

Exclusion criteria: patients with bone metabolic diseases other than osteoporosis, hyperparathyroidism, osteomalacia, hypocalcemia, significantly impaired renal function (serum creatinine >1.3 mg/dl), evidence of significant organ diseases, patients in treatment with oestrogens.

Study design

Patients were randomized with ratio 1:2 into 2 groups (A and B) and the study was conducted in an open manner even if both densitometrical and biochemical evaluations were carried out by a technician not aware of the treatment assignment.

Group A was treated with daily calcium at the dose of 1000 mg and vitamin D at the dose of 800 IU for 12 months.

Group B was treated with monthly intramuscular NE at the dose of 25 mg added to daily calcium (1000 mg) and vitamin D (800 IU) for 12 months.

All patients were assessed at the beginning of the study (M0) and 12 months after (M12) by measuring lumbar spine (L1-L4) and left proximal femur BMD using dual energy x-ray absorptiometry (DXA) with Hologic QDR 4500 (Waltham, MA, USA). The lumbar vertebrae with fractures or deformities were excluded from analysis. Quality control was maintained by the daily scanning of an anthropomorphic spine phantom. The precision is 1% for lumbar spine and <1.5% for proximal femur BMD.

At M0, M6 (6 months after start of treatment) and M12, all patients underwent blood tests and urine analysis. The monitored parameters were: complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), protein electrophoresis, glycaemia, transaminase, creatininemia, standard urine test, serum total and bone alkaline phosphatase (B -ALP), serum intact parathyroid hormone (PTH 1-84), serum osteocalcin (OC), urine N-telopeptyde type 1 collagen (NTX), deoxypyridinoline (DPD), 24-hour calciuria, creatininuria second-morning urine (before 10 am), hydroxyprolinuria (OHPr).

Both densitometrical and biochemical evaluations were carried out by a technician who was not aware of the treatment assignment.

To evaluate differences in BMD changes according to CRP levels, we pooled together the patients of both Groups (A and B), excluding only those affected by SLE where CRP is usually negative, then we calculated the median CRP (mg/dl) at M0 and we divided patients into two additional subgroups without any difference in the GC treatment dose. Subgroup 1 that included patients with CRP lower than median and Subgroup 2 that comprised patients with CRP higher than median.

Collection and storage of samples

Blood samples for the study were drawn using standard venipuncture technique between 08:00 and 09:00 am after an overnight fast. Peripheral venous blood was drawn into sterile vacuum blood collection tubes without any additives for serum samples and into K_3-EDTA vacutainer tubes for plasma samples (Becton Dickinson, San Jose, CA, USA). Serum was separated after centrifugation of blood at 4°C, 1500 g for 10 minutes.

Urine samples were obtained from a 24-hour urine specimen including the early morning portion. Patients were instructed to collect their urine for 24 hours.

After division into aliquots, serum, plasma and urine samples were immediately analysed or frozen and stored at -80°C until assay, and were thawed only once.

Biochemical measurements

Erythrocyte sedimentation rate (ESR) was measured on the Ves-Matic 20 automatic instrument (DIESSE – Diagnostica Senese, Siena, Italy).

Levels of serum and urinary calcium, creatinine and phosphate, serum alkaline phosphatase, albumin and C-reactive protein (CRP) were measured using commercially available kits (Olympus Diagnostici, Italy) run on an Olympus AU400® chemistry autoanalyser (OLYMPUS Instruments, Japan).

Serum bone-specific alkaline phosphatase (B-ALP) level was assayed using a Metra BAP EIA kit (Quidel, San Diego, CA, USA). The intra-assay and interassay coefficients of variation for bone-specific alkaline phosphatase were less than 5% and 8%, respectively.

Plasma intact parathyroid hormone (PTH) was measured by a solid-phase, two site chemiluminescent enzyme-labeled immunometric assay on the IMMULITE® automated analyser (Diagnostic Products Corporation, Los Angeles, CA, USA).

Plasma osteocalcin (OC) was measured by an electrochemiluminescence sandwich immunoassay on the fully automated analyser Modular® analytical system platform (Roche Diagnostics, Milan, Italy). The detection limit for osteocalcin was 0.5 ng/ml, and the intra-assay and interassay coefficients of variation ranged from 3.8% to 6.7%, respectively.

Urine deoxypyridinoline (DPD) assay was performed with a solid-phase chemiluminescent enzyme-labeled immunoassay (Pyrilinks-D) on a multianalyte automated analyzer IMMULITE® 2000 (manufactured by DPC and purchased from Medical Systems SpA, Genoa, Italy). Data are expressed as the ratio to creatinine concentration. The within- and between-run imprecision for DPD cross-link measurements were 4.4% and 8.7%, respectively. The intra- and interseries variations in urine creatinine assay were 1.2% and 1.8%, respectively.

Urinary cross-linked N-telopeptides of bone type I collagen (NTX) was measured with Osteomark NTx (Ostex International Inc, Seattle, WA, USA; purchased from Bouty, Milan, Italy). Results in the biological variability

studies were corrected for differences in urine concentrations by expression relative to the urinary creatinine concentration. For the Osteomark NTX serum assay, the CVs of the intra- and inter-assay variations, were 5.2% and 7.4%, respectively.

Hydroxyprolinuria (OHPr) was measured on the second urine collection of the day in fasting patients by a technique involving hydrolysis, purification on resin, separation by high performance liquid chromatography (HPLC) and fluorescence detection (Bracco, Merck). Coefficient of variation was 6.1%. Prior to hydroxyproline measurement patients were advised to remain on low collagen diet during the 24-hour period of urine collection and also the previous 48 hours (instructions were given to avoid gelatinous foods, meat, fish and other non-vegetarian preparations).

Statistical analysis

Sample size estimation

Rheumatic patients treated with NE for one year showed a lumbar BMD improvement of 3.7% from baseline (21, 22). The same trend was observed from a pilot study carried out by the Authors, in which the 12 month-baseline difference in lumbar BMD levels between NE and control groups was 0.031 mg/dl with a standard deviation of 0.042. Considering a type I and II error of 0.05 and 0.20 respectively, and a 2:1 ratio in favour of the intervention arm for ethical reasons, the sample size needed to point out the expected difference 69 patients.

Baseline characteristics between groups were tested for any difference by means of unpaired Student *t*-test or by Fisher's exact test where appropriate.

Repeated measures analysis of variance was used to assess changes in lumbar and femoral BMD from baseline to M12 and to compare different trends between Groups A and B. The same analysis was applied to test trends over time from baseline to M12 of the variables that were recorded also after 6 months of therapy. All data are presented as mean ± standard deviation. Significance level was set at 0.05. Statistical analysis was performed by means of SPSS statistical software 15.0.

Table I. Mean±SD of baseline characteristics in patients of both groups.

	Group A (n=23)	Group B (n=46) NE	Statistical significance*
Age	65.8 ± 8.7	67.5 ± 9.7	n.s
Disease duration (months)	31.6 ± 18.4	35.9 ± 21.1	n.s.
Steroid treatment duration (months)	28.6 ± 19.7	32.7 ± 25.01	n.s.
Steroid daily dose in mg (6-methylprednisolone)	6.01 ± 2.52	6.37 ± 2.84	n.s.
Lumbar BMD t-score	-2.52 ± 0.85	-2.74 ± 0.86	n.s.
Femoral BMD t-score	-2.19 ± 0.90	-2.16 ± 0.65	n.s.
CRP (mg/dl) normal value <0.5 mg/dl	1.0 ± 1.21	1.23 ± 0.97	n.s.
RA (n=27)	10	17	n.s.
Polymialgia rheumatica (n =20)	6	14	n.s.
Sjögren's syndrome (n=15)	5	10	n.s.
Seronegative arthritis (n=5)	1	4	n.s.
SLE (n=2)	1	1	n.s.

*Unpaired student's *t*-test or Fisher's exact test as appropriate

Table II. Mean % BMD changes in patients with CRP ≤0.9 mg/dl and patients with CRP >0.9 mg/dl.

BMD changes in 12 months	CRP (mg/dl)	Group A (n=22)	Group B (n=45)	*p*
Lumbar	≤0.9 (sub-group 1)	-1.90% (n=14)	+3.64% (n=19)	<0.01
	>0.9 (sub-group 2)	- 5.53% (n=8)	+3.05% (n=26)	<0.001
Femoral neck	≤0.9 (sub-group 1)	-2.01% (n=14)	+2.94% (n=19)	<0.01
	>0.9 (sub-group 2)	- 3.67% (n=8)	+0.80% (n=26)	n.s.

Results

We enrolled 69 Caucasian patients (66 females, 3 males) aged between 48 and 81 (mean age 66.9±9.32 years) in GC chronic treatment for rheumatic diseases. Twenty-seven were affected by rheumatoid arthritis, 20 by polymialgia rheumatica, 15 by Sjögren's syndrome, 5 by seronegative arthritis, and 2 by SLE. Twenty-nine patients (9 in group A and 20 in group B) had received an oral BP up to 6 months before the start of the trial and developed intolerance in the first 4 weeks of treatment.

The baseline characteristics of the study population are shown in Table I.

All 69 patients completed the 1-year follow-up continuing the stabilized dose GC therapy at the same.

NE was generally well tolerated. Four patients in treatment with NE developed a transient acute phase reaction (fever up to 38°C, general and muscle pain, headache) immediately after the first injection of NE: this adverse effect occurred only with the first injection and all 4 patients could continue the treatment. Twenty-seven Group B patients developed local pain at the site of injection, lasting less than 15 minutes. Seven Group A patients and 17 Group B patients declared a transient nausea or gastralgia caused by calcium. No significant biohumoral side effects emerged from the monitoring of complete blood count, glycaemia, transaminase, creatininemia and urine.

At M12, both lumbar and femoral neck BMD decreased respectively of 2.97% (p=0.001) and 2.40% (p=0.04) versus baseline (M0) in Group A, and increased respectively of 3.34% (p=0.001) and 1.78% (p=0.09) in Group B.

The difference in BMD change at the lumbar spine between Group A and Group B was 6.31% (p=0.001), while difference in BMD change at femoral neck was 4.18% (p=0.01).

The CRP median (mg/dl) of 67 patients (excluding the 2 patients affected by SLE, one for each group) was 0.9 mg/dl. We divided the patients of both Groups A and B in 2 Subgroups: Subgroup 1 including patients with CRP ≤0.9 mg/dl and Subgroup 2 with CRP >0.9 mg/dl.

NE resulted effective in both Subgroup patients; in particularly in those patients with CRP >0.9 mg/dl where

Table III. Mean ± SD change of bone markers in patients of both group (comparison versus M0. *p<0.05; **p<0.01;***p<0.001)

	Group A n=23 Group B n=46	M 0	M 6	M 12
OHPr/ Creatininuria (normal value <0.025)	A	0.027 ± 0.005	0.026 ± 0.006 (-3.70%)	0.028 ± 0.004 (+3.70%)
	B	0.029 ± 0.007	0.017 ± 0.005 (-41.64%)***	0.018 ± 0.003 (-37.91%)***
DPD /Creatinine (normal value <7)	A	8.57 ± 2.23	8.48 ± 1.65 (-1.05%)	8.03 ± 1.74 (-6.30%)
	B	8.62 ± 2.48	5.74 ± 1.43 (-33.4%) ***	5.77 ± 1.32 (-33.18%) ***
NTX/ Creatininuria (normal value <47)	A	64.31 ± 25.78	60.05 ± 22.95 (-6.62%)	58.87 ± 19.46 (-8.46%)
	B	71.58 ± 30.01	30.87 ± 9.64 (-57.8%)***	33.69 ± 7.77 (-55.95%)***
OC (ng/ml; normal value 1.1–7.2)	A	5.13 ± 2.84	5.37 ± 1.88 (+4.68%)	5.46 ± 1.65 (+6.43%)
	B	4.99 ± 2.27	4.41 ± 1.79 (-11.62%)	4.36 ± 1.49 (-12.62%)
B-ALP (UI/L; normal value 10-22)	A	19.01 ± 7.9	20.04 ± 5.4 (+5.42%)	21.17 ± 4.9 (+11.46%)
	B	17.75 ± 8.4	15.27 ± 3.71 (-13.95%)*	17.59 ± 2.42 (-0.85%)
PTH 1-84 (pg/ml; normal value 10-75)	A	50.09 ± 16.0	46.66 ± 15.2 (-6.85%)	47.55 ± 14.7 (-5.07%)
	B	44.43 ± 15.4	51.04 ± 15.1 (+14.88%)***	47.84 ± 13.2 (+7.66%)
Calciuria/Creatininuria (normal value <0.20)	A	0.19 ± 0.06	0.19 ± 0.05 (0.0%)	0.18 ± 0.05 (-5.26%)
	B	0.20 ± 0.07	0.15 ± 0.04 (-25.00%) ***	0.19 ± 0.05 (-5.00%)

lumbar BMD change between Group A and Group B was 8.58% (p<0.001), as reported in Table II.

Bone markers were also measured at M0, M6 and M12.

In Group A we did not observe any significant change in levels of OHPr, DPD, NTX, OC, B-ALP, PTH and calciuria. In group B, markers of bone resorption decreased significantly at M6 and M12 with a transient significant increase of PTH at M6.

Data concerning bone markers are shown in Table III and Figure 1.

Discussion

One year of monthly intramuscular administration of NE at the dose of 25 mg in rheumatic patients under GCs treatment leads to a significant improvement (+3.34%; p=0.001) of lumbar BMD and prevents femoral and neck bone loss.

This result is somewhat close to those obtained by the administration of oral risedronate at the daily dose of 2.5 mg and oral alendronate at the daily dose of 10 mg in patients affected by rheumatic diseases and treated with a similar low-dose of GCs (31, 32, 33).

In post-menopausal osteoporosis Braga *et al*. found an improvement in lumbar BMD of 7.4% after 24 months (19), when administering bimonthly intravenous NE at the dose of 50 mg; in addition, in the NEOP-1 study monthly im 25 mg caused a lumbar BMD improvement of 5.25% in 12 months (21, 22).

Our data concerning improvement of femoral neck BMD (+1.78%), skeletal site of cortical bone, reach the statistical significance (p=0.01) if we calculate the difference of BMD between Group A and Group B.

It is known that BMD changes are generally larger in the spine than in the hip, because of the different composition in trabecular and cortical bone. Using oral alendronate, Tascioglu found in the hip an improvement of 0.8% (33), while Lems showed an improvement of 0.94% (32) after 12 months.

Concerning CRP levels we found a relationship with BMD changes. In 1998 Gough demonstrated that in patients affected by rheumatoid arthritis CRP levels are closely correlated to BMD changes, as CRP levels are a good marker for the activity of RA (34). In our patients the correlation was present even if affected by various inflammatory rheumatic diseases. CRP is an acute phase reactant, directly related to interleukin 6 (IL-6) which increases in response to tissue damage, inflammation and infections: IL-6 is a cytokine which is considered as a potent mediator of the inflammatory process (35).

As reported in Table II, we observed the greatest improvement in lumbar and femoral neck BMD (Group B) in patients with low CRP levels (+3.64% lumbar BMD), while the major BMD loss in Group A (-5.53% lumbar BMD) was linked to high CRP levels. These data support the notion that cytokines, which are abundantly produced in the course of inflammatory rheumatic diseases, have been recognized as playing an important role in determining osteoporosis (36). Our data also showed the efficacy of im NE in the subgroup with higher CRP (+3.05% lumbar BMD), in which the lumbar BMD change between Group A and Group B was 8.58% (p<0.001).

Concerning bone resorption markers (see Table III), the lack of significant reduction of bone remodelling markers in patients of group A is not surprising: in GIO bone turnover generally is just low and calcium/vitamin D alone are not sufficient for a further suppression. Also in the study of Lems *et al*. (32) a lack of significant reduction of bone turnover markers was observed in the calcium/vitamin D group. Conversely, in group B NTX and DPD decreased significantly at M6 and M12, very similarly to the results obtained with daily oral alendronate and risedronate (31-33)

On the other hand, in our study OC reduction did not reach significance at M6 (p=0.05) nor at M12 (p=0.06), while with risedronate and alendronate the reduction was greater and statistically significant (31-33). Moreover, B-ALP had only a transitory decrease at M6 (p=0.04), in contrast with the trend observed using risedronate and alendronate (31-33). Both data are consistent with the results obtained *in vitro* by

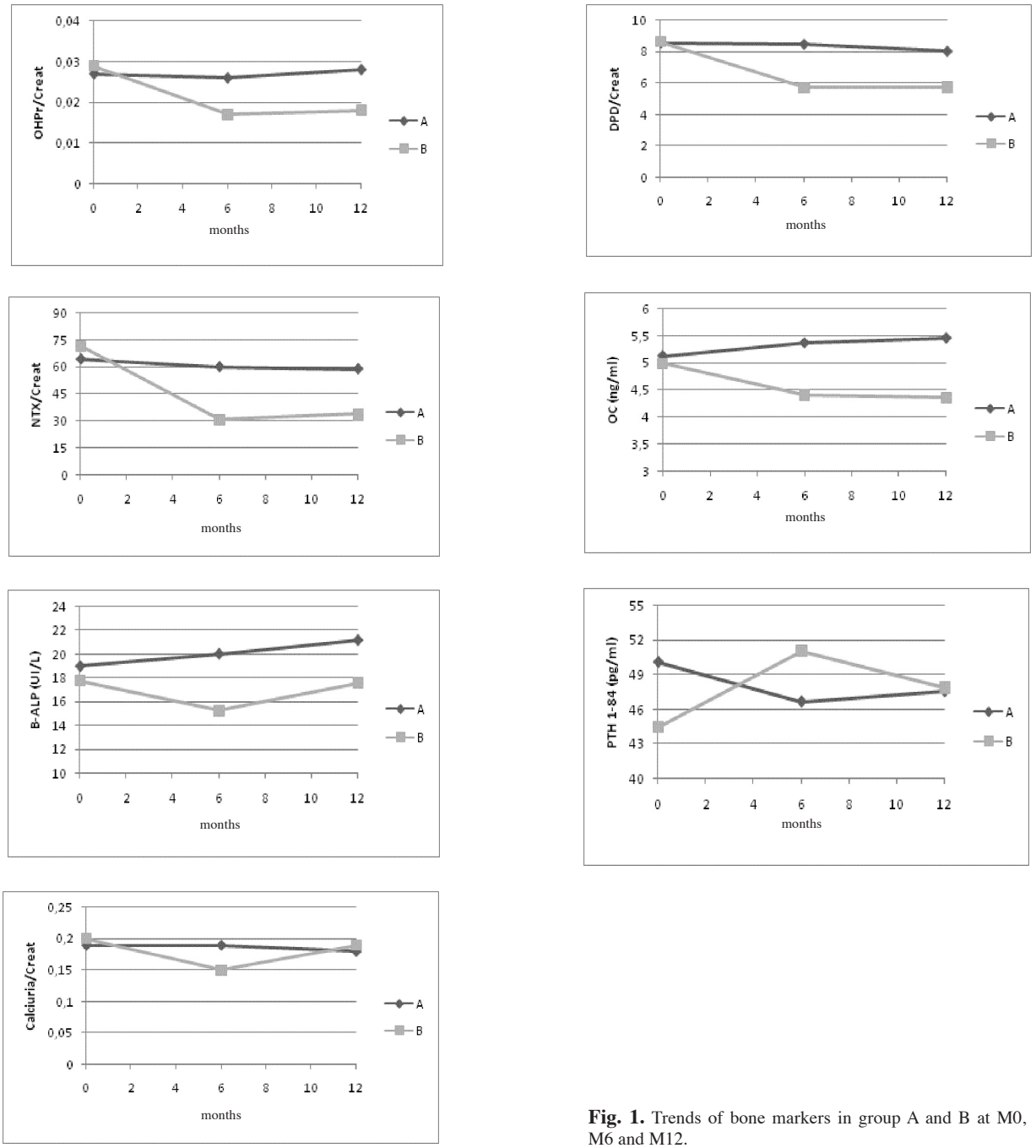

Fig. 1. Trends of bone markers in group A and B at M0, M6 and M12.

Frediani. This Author found that NE at therapeutic doses does not affect the viability, proliferation and cellular activity of normal human osteoblasts and that it seems to enhance the differentiation of cultured osteoblasts in mature bone-forming cells (37-38). As *in vivo* the metabolic effects of BPs are due to the reduction of the number of bone remodelling units we assume that NE could compensate the reduction of bone remodelling units because of its peculiar effects on osteoblasts (38-39).

Concerning PTH (see Table III), we found a transient significant increase at M6: as calcium usually leads to a reduction in PTH, this could be a peculiar characteristic of NE in rheumatic patients under low-dose GCs therapy. Unfortunately, there is no other report about PTH levels in course of treatment with NE. However, Jacobs found an increase of PTH using oral alendronate and calcium to prevent GIO (40).

Intravenous BPs are now available: their administration (every 3 or 12 months) can increase patients' adherence; however, side effects of intravenous BP are under discussion (41). Moreover, monthly intramuscular NE can be easily administered at home, without hospitalising patients and thus decreasing the charge on the National Health Service.

In conclusion, we have shown that monthly intramuscular administration of NE at the dose of 25 mg, added to calcium and vitamin D, is effective in preventing GIO in rheumatic patients

under chronic treatment with low-dose steroids. NE is effective even in those patients with high CRP levels. NE reduces bone resorption, while some data may imply a lower impact on bone formation. Moreover, the intramuscular route of administration is generally well tolerated and could increase patients' adherence.

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