

Can neridronate be effective in the treatment of osteoporosis in hypogonadic men?

Sirs,

Neridronate (NE), 6-amino-1-hydroxyhexylidene-1,1-bisphosphonate, is a third-generation bisphosphonate, which is indicated only for the treatment of osteogenesis imperfecta (1-2). However, several recent papers showed that NE can also be effective in the treatment of post-menopausal osteoporosis (3-4), glucocorticoid induced osteoporosis (5), Paget's disease (6), and transient osteoporosis of the hip (7).

Here, we report two cases of osteoporotic middle-aged men, both affected by hypogonadism, with previous vertebral (and, in case no.1, also wrist) fractures, treated for 12 months with i.m. neridronate at the dose of 25 mg every 30 days. Both patients showed increased spine Bone Mineral Density (BMD) and, in case no.1, also hip BMD. Lumbar and femoral BMD was evaluated by dual energy x-ray absorptiometry (DEXA). *Case no. 1:* A Caucasian school caretaker, 51-year-old, non-drinker, non-smoker, affected by anamnestic hypogonadism with azoospermia and short-stature. For these reasons, he had not been enlisted in the army. At the age of 24, he fractured his left wrist and, at the age of 34, he fractured several thoracic and lumbar vertebrae. His first treatment was with testosterone i.m. at the dose of 250 mg weekly. At the age of 50, he also fractured his right wrist. In 1999, his lumbar BMD T-score was -5.3 SD; hip BMD -4.7 SD. In 2001 (at the age of 49), he came for a rheumatological examination. A blood sample showed only a high γ GT (never explained), while other laboratory tests showed normal range values, including ALT, AST, ALP, PTH, LH, FSH, prolactin and PSA.

He suffered disabling back-pain. His lumbar BMD T-score worsened to -5.7 SD and hip BMD to -4.8 SD. We decided to treat him with an orthopaedic jacket, and with oral alendronate at the dose of 70 mg once a week, added to testosterone i.m. at the dose of 250 mg weekly, calcium 1000 mg/daily and vitamin D 800 UI/daily. In 2004, at the age of 52, his lumbar BMD T-score further worsened to -5.9 SD, Z-score -5.5 SD, while hip BMD improved to -3.6 SD, Z-score -3.3 SD. We stopped alendronate and started a new treatment as follows: testosterone i.m. 250 mg weekly, neridronate 25 mg i.m. monthly, calcium 1000 mg/daily and vitamin D 800 UI/daily. After 1 year, his lumbar BMD T-score had improved to -5.3 SD (+13.9%; following Least Detectable Change criteria + 10%), Z-score -4.9 SD, and hip BMD to -3.4 SD (+6.9%; following Least Detectable Change criteria + 3.3%), Z-score -3.0 SD (8.9). No side-effects were present. The patient is still continuing the treatment with a marked improvement in his quality of life.

Case No. 2: A Caucasian teacher, 51 year-

old, with two daughters. According to his medical history he was a non-drinker and non-smoker. At the age of 31, the first diagnosis of osteopenia was made and he began to take calcium 1000 mg/day and vitamin D 800 UI/day. For a decreased lumbar spine BMD (T-score -2.10 SD Z score -1.87 SD) he also took alendronate 70 mg/once a week for one year. At the age of 50, he observed a decrease in libido and in penile erection, followed by anosmia and, more recently, loss of moustache and eyebrows. Then he fractured the vertebral body of T12. For the latter reasons, a rheumatological consultation was carried out. The patient was 182 cm tall and weighed 63 kg. After 6 months of treatment with testosterone at the dose of 100 mg i.m. every 15 days, his lumbar BMD T-score was decreased to -2.51 SD, Z score -2.11 SD, hip BMD was T-score -1.91 SD, Z-score -1.61 SD. Routine tests showed normal values including prolactin, 17- β -estradiol, progesterone, DHEA-S, PTH, TSH, bone-ALP, calcium and phosphorus, while the following tests were out of range: cross-laps 7876 pM, D-pyridinoline/urinary creatinine 8.9, NTX/urinary creatinine 55, FSH 0.6 (reference values 1.4-18 UI/l) LH 0.7 (reference values 1.4-7.7 UI/l) testosterone 4.6 (reference values 8.4-28 nM/l). MR of the brain with contrast medium in coronal scansion showed hypotrophy of both olfactory bulbs. The final diagnosis was: hypogonadotropic hypogonadism in late-onset Kallmann's syndrome (10). The treatment was the following: Neridronate at the dose of 25 mg i.m. monthly in addition to testosterone 100 mg i.m. every 15 days. After 12 months his lumbar BMD T-score improved to -2.1 SD (+4.2%, following Least Detectable Change criteria +0.82%), Z-score -1.87 SD, hip BMD T-score was -1.88 SD (following Least Detectable Change criteria not significative value), Z-score -1.58 SD (8.9). Bone turnover markers also improved as follows: cross-laps 2378 pM, D-Pyridinoline/urinary creatinine 6.6, NTX/urinary creatinine 27, testosterone 6.2 nM/l.

These two case-reports confirm that hypogonadism is one of the possible causes of osteoporosis in men, which should always be taken into serious consideration in the differential diagnosis. In these cases, substitution therapy with androgens is necessary, but probably not always enough to recover the loss of bone mass. On the contrary, in our case-reports the addition of NE i.m. administration has been effective and seems to be able to replace lumbar bone loss in a relatively short time. Other authors (4) observed that intermittent NE i.m. administration has been more effective than oral bisphosphonates in the treatment of osteoporosis in elderly women: it is interesting to stress that in both our cases, oral bisphosphonates used before NE treatment did not improve lumbar BMD.

In other papers, NE was effective in preventing bone loss in men receiving androgen deprivation therapy for prostate can-

cer: we can say that our cases, affected by hypogonadism, were probably in a similar condition (11, 12). Moreover, in our second case we observed a reduction of bone resorption markers such as demonstrated in another paper (13).

These mechanisms may be responsible for the anabolic effect and increase of BMD in male osteoporosis.

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References

- GATTI D, VIAPIANA O, LIPPOLIS I *et al.*: Intravenous bisphosphonate therapy increases radial width in adults with osteogenesis imperfecta. *J Bone Miner Res* 2005; 20: 1323-6.
- GATTI D, ANTONIAZZI F, PRIZZI R *et al.*: Intravenous neridronate in children with osteogenesis imperfecta: a randomized controlled study. *J Bone Miner Res* 2005; 20: 758-63.
- BRAGA V, GATTI D, COLAPIETRO F *et al.*: Intravenous intermittent neridronate in the treatment of postmenopausal osteoporosis. *Bone* 2003; 33: 342-5.
- CASCELLA T, MUSELLA T, ORIO F JR *et al.*: Effects of neridronate treatment in elderly women with osteoporosis. *J Endocrinol Invest* 2005; 28: 202-8.
- BENUCCI M, DOLENTI S, SAVIOLA G, MANFREDI M: Modifications of markers of bone resorption in patients affected by Glucocorticoid Induced Osteoporosis (GIO) treated with Neridronate. *Recenti Prog. Med* 2006; 97: 24-7.
- ADAMI S, BEVILACQUA M, BROGGINI M *et al.*: Short-term intravenous therapy with Neridronate in Paget's disease. *Clin Exp Rheumatol* 2002; 20: 55-8.
- LA MONTAGNA G, MALESCI D, TIRRI R, VALENTINI G: Successful neridronate therapy in transient osteoporosis of the hip. *Clin Rheumatol* 2005; 24: 67-9.
- EL MAGHRAOUI A, DO SANTOS ZOUNON AA, JROUNDI I *et al.*: Reproducibility of bone mineral density measurement using dual x-ray absorptiometry in daily clinical practice. *Osteoporosis Int* 2005; 16: 1742-8.
- LODDER MC, LEMS WF, ADER HJ *et al.*: Reproducibility of bone mineral density measurement in daily practice. *Ann Rheum Dis* 2004; 63: 285-9.
- NACHTIGALL LB: Adult onset idiopathic Hypogonadotropic Hypogonadism-A treatable form of male infertility. *N.Eng. J. Med* 1997; 336: 410-15.
- MAGNO C, ANASTASI G, MORABITO N *et al.*: Preventing bone loss during androgen deprivation therapy for prostate cancer: early experience with neridronate. *Eur Urol* 2005; 47: 575-80.
- MORABITO N, GAUDIO A, LASCO A *et al.*: Neridronate prevents bone loss in patient receiving androgen deprivation therapy for prostate cancer. *J Bone Miner Res* 2004; 19: 1766-70.
- MAZZANTINI M, DI MUNNO O, METALLI MR, BULLERI M, GIORDANI R: Single infusion of Neridronate (6-amino-1-hydroxyhexylidene-1,1-bisphosphonate) in patients with active rheumatoid arthritis: effects on disease activity and bone resorption markers. *Aging Clin Exp Res* 2002; 14: 197-201.