

**NERIDRONIC ACID EFFECTS IN POSTMENOPAUSAL OSTEOPOROSIS:
TREAT AND ADHERE ANYWAYS**

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Abstract:

Osteoporosis is a major health concern that is associated with an increased risk of first and subsequent bone fractures. Untreated osteoporosis results in considerable morbidity. Currently, bisphosphonates are the mainstay of treatment for osteoporosis and the aim of this study was to assess the effects of intravenous (IV) and intramuscular (IM) neridronate (NE) on femoral/lumbar bone mineral density (BMD) and fracture risk in patients with postmenopausal osteoporosis. Data were collected on age, weight, body mass index, physical activity, smoking, height loss, history of falls, total hip and lumbar BMD, and creatinine clearance. Inclusion criteria were a lumbar or femoral BMD T score < 2.5; Exclusion criteria were secondary osteoporosis, previous osteoporotic fracture, prior bisphosphonates or osteoporosis medications other than calcium or colecalciferol, presence of any concomitant skeletal metabolic disease.

METHODS: 164 patients (mean age 64±2.7 years) with postmenopausal osteoporosis confirmed with a lumbar and femoral DEXA BMD scan received NE IV 100mg every 8 weeks for 18 months and subsequently IM NE 25 mg every 4 weeks for 18 months. All patients had gastric or esophageal conditions that contraindicated treatment with oral bisphosphonates (BPs). All subjects received daily calcium 1 g and vitamin D 800 UI. Lumbar and femoral DEXA BMD scans were performed at baseline, 18 months and 36 months.

RESULTS: After 18 months of IV therapy mean ±SD lumbar BMD was significantly increased (baseline -2.8±1.2 vs 18 months -2.6±1.4; p<0.01). Mean ±SD femoral neck BMD was also improved (baseline -2.15±1.1 vs 18 months -2.01±0.5; p<0.05). After an additional 18 months of IM NE the mean ±SD BMD values were lumbar -1.89±0.8 and femur -1.49±1.48; p< 0.01 vs. baseline.

CONCLUSION: The results of this study confirm the role of NE in the treatment of postmenopausal osteoporosis and indicate the potential usefulness of intramuscular administration in the treatment of these patients.

Key Words: Postmenopausal osteoporosis, Neridronate, Bone mineral density, Bisphosphonate

Introduction

Osteoporosis is a chronic disease affecting an estimated 200 million people worldwide, resulting in bone fragility due to a decrease in the mass and deterioration of the microarchitecture of bone. It is often diagnosed only after a first fracture.^{1,2} Osteoporosis can be classified as primary or secondary. The primary form results from age-associated changes in sex hormones and can be subdivided into primary type 1 or postmenopausal osteoporosis, and primary type 2 or senile osteoporosis, which occurs after age 75 in both men and women. Secondary osteoporosis can be caused by variety of pathological conditions, or result from long-term therapy with drugs that adversely affect bone metabolism.³

The World Health Organization defines osteoporosis as a bone mineral density (BMD) T-score that is >2.5 standard deviations below the gender-specific young adult mean as measured by dual energy X-ray absorptiometry (DEXA).⁴ Overall fracture risk is also influenced by BMD-independent risk factors. Absolute fracture risk can be estimated using the FRAX algorithm, which provides a 10-year probability of osteoporotic fracture by considering also information on patient characteristics (age, body mass index, rheumatoid arthritis), behaviors (smoking, alcohol intake, corticosteroid use) and personal or parental history of fractures.^{5,6}

Osteoporosis is usually treated with bisphosphonates. This class of drugs acts on osteoclasts, the cells responsible for bone re-absorption, and functions by inhibiting their recruitment and reducing their life span and activity.⁷ Bisphosphonates are currently available in several formulations. Alendronate (ALN), risedronate (RIS), and ibandronate (IBN) are oral bisphosphonates widely used for the treatment of postmenopausal osteoporosis. Standard regimens include ALN or RIS once-weekly, IBN or RIS once- or twice-monthly, intravenous (IV) IBN four time per year and IV zoledronate once per year.

Neridronate (NER) is an amino-containing bisphosphonate with a chemical structure similar to that of ALN. These two drugs differ in the number of methyl groups in the R2 side chain: ALN has three, while NER has five. Neridronate is licensed for the treatment of osteogenesis imperfecta and Paget's disease.⁸ Nevertheless, NER IV has shown a remarkable efficacy also for postmenopausal osteoporosis.⁹ In the present study we assess the efficacy and the safety of NER IV and intramuscular (IM) in patients with postmenopausal osteoporosis.

Patients and methods

Between Jan 2007 and Jan 2011 all outpatients with osteoporosis assessed with a lumbar and femoral DEXA BMD scan and diagnosed as postmenopausal by a rheumatologist specializing in metabolic bone diseases (L.A.) were enrolled in our study. All patients enrolled had gastric or esophageal conditions that contraindicated treatment with oral bisphosphonates. 164 patients (mean age 64 ± 2.7 years) were recruited. All subjects received 1 g of calcium and 800 UI of vitamin D, daily. Lumbar and femoral DEXA BMD scans were performed at baseline, 18 months and 36 months. All patients received also 100 mg NER IV bimonthly for the first 18 months, infused in a 0.9% saline solution over the course of 150 min. Subsequently, all patients received 25 mg NER IM monthly from month 18 to 36.

DEXA (Hologic QDR-9000, Hologic Inc., Bedford, MA, USA) was used to measure hip and lumbar spine (L1-L4) and femoral (total and neck) BMD at enrollment, and then after 18 and 36 months. Standard dorsal and lumbar spine X-rays were assessed at baseline, and again at the 18- and 36-month scheduled visits. This study was approved by the local ethics committee. Written informed consent was obtained from each participant. The primary endpoints of this study were hip

and spine BMD modifications over the 18 months treatment with NER IV, as described above, and fracture status. The secondary endpoint was hip and spine BMD modifications over the subsequent 18 months of treatment with NER administered IM.

Results

After 18 months of IV NER therapy mean lumbar BMD was significantly increased (mean T score -2.8 ± 1.2 at baseline vs. -2.6 ± 1.4 at 18 months, $p < 0.01$). Mean femoral neck BMD T score was improved also (-2.15 ± 1.1 at baseline vs. -2.01 ± 0.5 at 18 months, $p < 0.05$). After the subsequent 18 months of IM NER (months 18 to 36) the mean lumbar BMD T score increased to -1.89 ± 0.8 and at the femur T score -1.49 ± 1.48 , $p < 0.01$). No vertebral fractures were evident on X-rays performed at 18 and 36 months.

Plasma levels of calcium were not influenced by the treatment and NER was well tolerated in this study. We observed rare benign, transient, self limiting post infusion reactions characterized by fatigue, fever and arthralgia.

DISCUSSION

While oral bisphosphonates effectively prevent bone loss and fractures, their administration is occasionally complicated by gastrointestinal complaints and the requirements for fasting and maintaining an upright posture for at least 30 minutes after administration to prevent irritation of the upper gastrointestinal mucosa. Some patients may find this regimen inconvenient.¹⁰

These issues may lead to reduced compliance,¹¹ a common problem in the treatment of chronic diseases in general.¹² Oral bisphosphonates also have the problem of limited bioavailability, reportedly less than 2% for alendronate and risedronate.¹³ Intravenous administration is an attractive solution for patients with gastrointestinal complaints or contraindications for oral preparations due to upper gastrointestinal tract abnormalities such as strictures, especially in the esophagus. IV administration is less complicated for the patient and assures compliance with therapy. It also provides a significant improvement over oral administration in terms of bioavailability.^{14,15}

The improvements that we have observed in mean lumbar spine and hip BMD values with respect to baseline both at 18 and at 36 months, as well as the lack of radiographic evidence of vertebral fractures suggest that this administration regimen for NER may reduce vertebral fractures and provide sustained BMD increases in patients with postmenopausal osteoporosis. Our findings are consistent with those of a randomized phase II 12-month study comparing various doses of IM neridronate to placebo in postmenopausal women with osteoporosis.¹⁶

Treatment was well tolerated, with symptoms of acute response observed rarely. These symptoms are known to occur after the first administration in as many as 10-30% of patients and are much less common after subsequent infusions, and with oral administration.¹⁷

Recently, the efficacy of NER administered IV has been compared to administration IM in patients with Paget's disease of bone.¹⁸ Administration of the same dose by these two routes was well tolerated and had similar effects on alkaline phosphatase as a marker of bone metabolism. While our study did not compare these routes directly, we did observe that the improvement in BMD provided by initial 18 months of IV administration in postmenopausal women was maintained and improved on during the subsequent 18 months of IM administration.

In conclusion, this study provides the first data on the efficacy and safety of NER in patients with postmenopausal osteoporosis and suggests administration of NER via IV or IM routes as alternative treatment for patients diagnosed with postmenopausal osteoporosis who have contraindications for oral bisphosphonates or experience gastrointestinal side effects when receiving oral bisphosphonates. These initial data encourage larger studies to examine its efficacy in preventing skeletal-related events such as vertebral fracture risk reduction, particularly trials with a non inferiority design.

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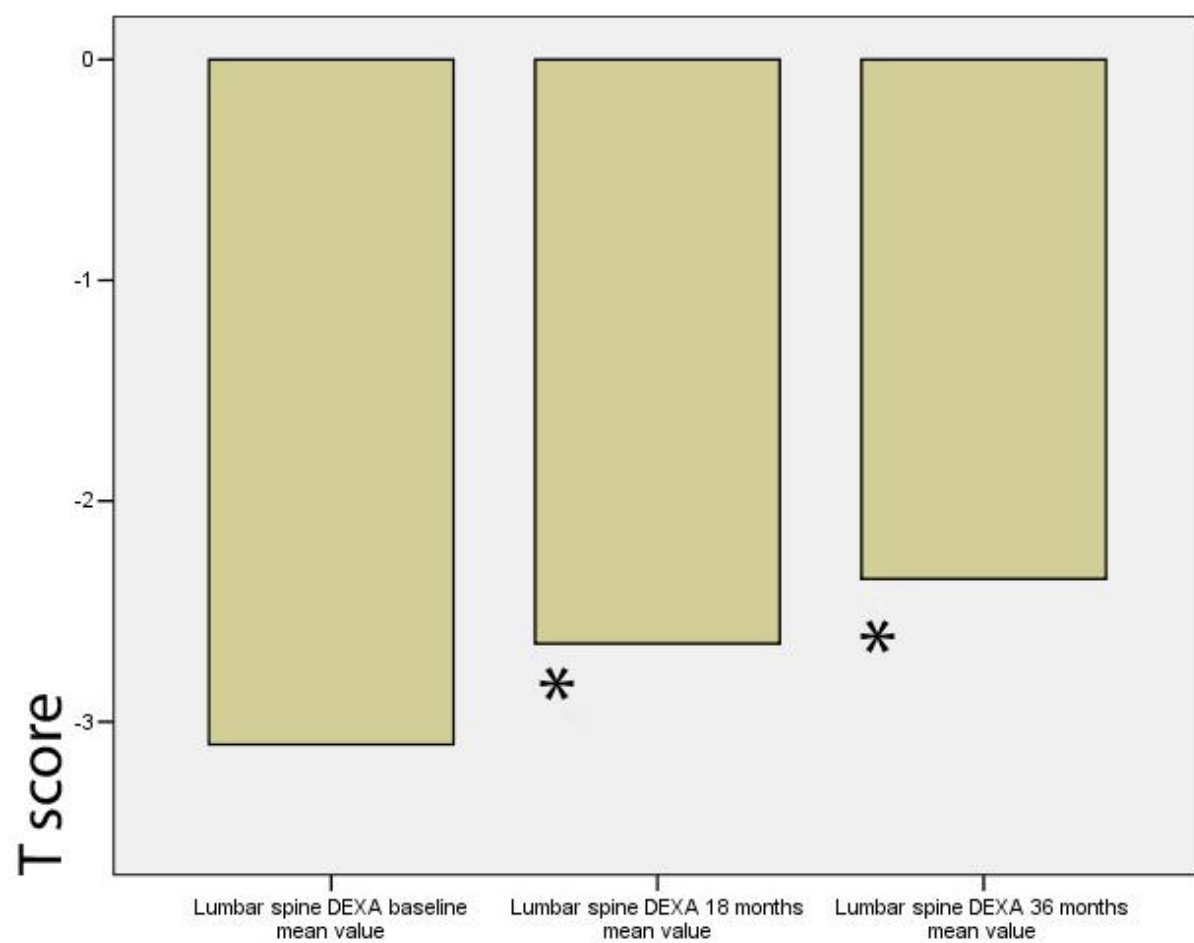
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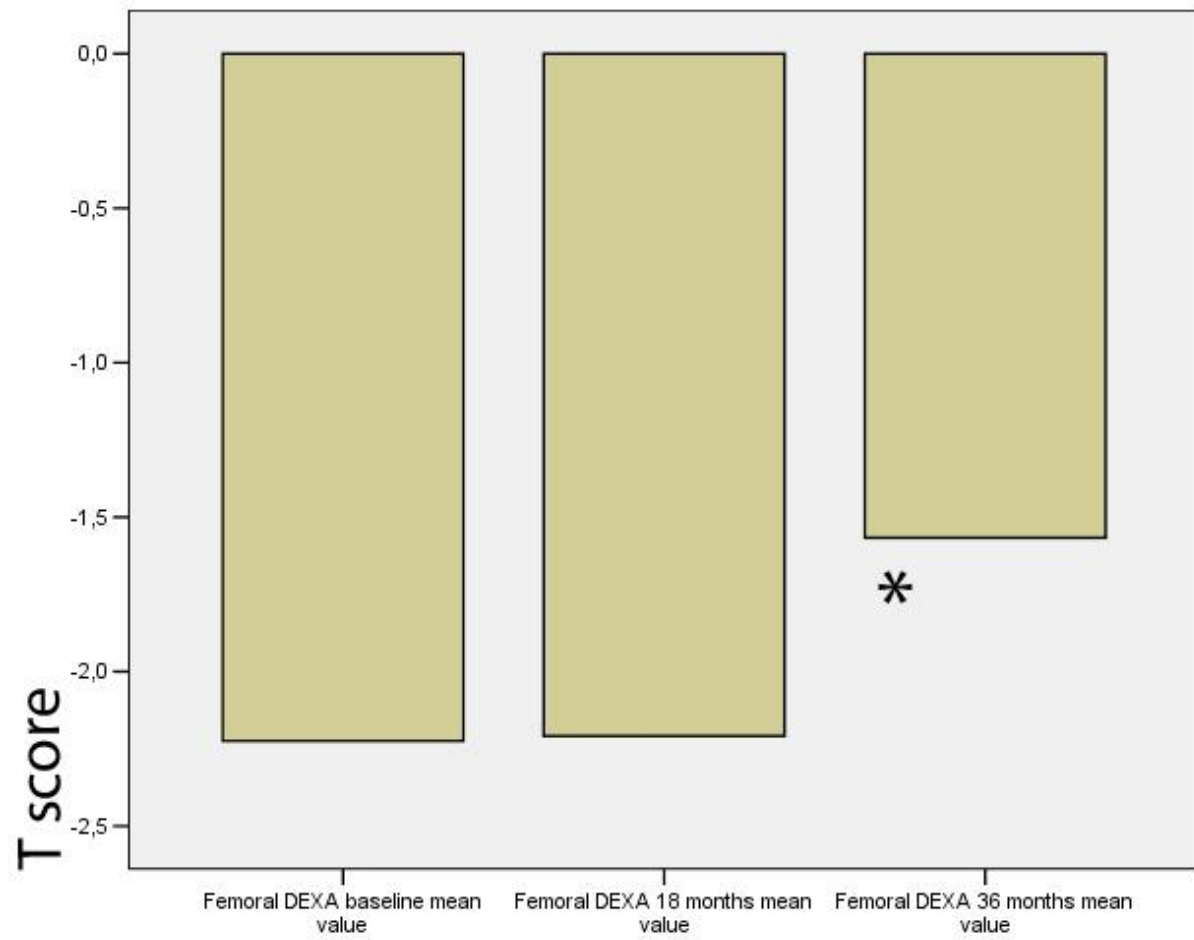
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179 Figure 1. Mean and 95% C.I. values of bone mineral density in i) lumbar spine and ii) femur,
180 measured by dual-energy X-ray absorptiometry at baseline, after 18 months of neridronate 100 mg
181 administered IV every 2 months, and after a subsequent 18-month period during which neridronate
182 (25 mg every month) was administered IM to patients with postmenopausal osteoporosis (n=64).

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