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Efficacy of Neridronic Acid IV and IM in Improving BMD and Reducing Fracture Risk in Postmenopausal Osteoporosis

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AL and MS designed the study and performed the statistical analysis, Authors DB and KR wrote the protocol. Authors KR and MGM wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Research Article

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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). 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

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months. Furthermore, the fracture risk FRAX was calculated at baseline and after 18 and 36 months of therapy.
Results: After 18 months of IV therapy mean ±SD lumbar T-score was significantly increased (baseline -2.8±1.2 vs 18 months -2.6±1.4; p<0.01). Mean ±SD femoral neck T-score 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 T-score values were lumbar -1.89±0.8 and femur -1.49±1.48; p< 0.01 vs. baseline. FRAX mean value was 14% for major osteoporotic fractures and 5.8% for hip fracture at baseline. After 18 months of therapy FRAX was 12% and 5%, respectively and finally at the end of the study was 10% for major osteoporotic fractures and 3.7% for hip fracture in the group treated continuously with NE IV and 9.8% and 3.9% in group treated with NE IM (P<0.05).
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.

Keywords: Neridronate; osteoporosis; fracture risk.

1. 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.

2. MATERIALS AND METHODS

Between Jan 2007 and Jan 2011 all outpatients with a not-previously treated osteoporosis (defined as DEXA T score of ≦ -2.6) 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 as gastroesophageal reflux disease or gastritis. Patients with other osteometabolic diseases or neoplasm were excluded. 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 500cc of 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. All authors hereby declare that this study have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. 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. The secondary endpoint was hip and spine BMD modifications over the subsequent 18 months of treatment with NER administered IM.

3. RESULTS AND DISCUSSION

After 18 months of IV NER therapy mean lumbar T-score was significantly increased (mean -2.8±1.2 at baseline vs. -2.6±1.4 at 18 months, $p<0.01$). Mean femoral neck 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 T score increased to -1.89±0.8 and at the femur T score -1.49±1.48, $p< 0.01$) (Fig. 1). No vertebral fractures were evident on X-rays performed at 18 and 36 months.

The ten year probability of fracture FRAX mean value was 14% for major osteoporotic fractures and 5.8% for hip fracture at baseline and 10% for major osteoporotic fractures and 3.7% for hip fracture after 36 months of therapy.

Furthermore also the absolute mean Bone Mineral Density (BMD) value increased during all the study period (lumbar values: baseline 0.761±0.21; 18 months 0.927±0.11; 36 months 1.148±0.18. Femural values: baseline 0.88±0.17; 18 months 0.96±0.13; 36 months 1.224±0.12. (Fig. 2)

Plasma levels of calcium were not influenced by the treatment and NER was well tolerated in this study. We observed rare (7 cases, 4.26% of patients) benign, transient, self limiting post infusion reactions characterized by fatigue, fever and arthralgia.

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].

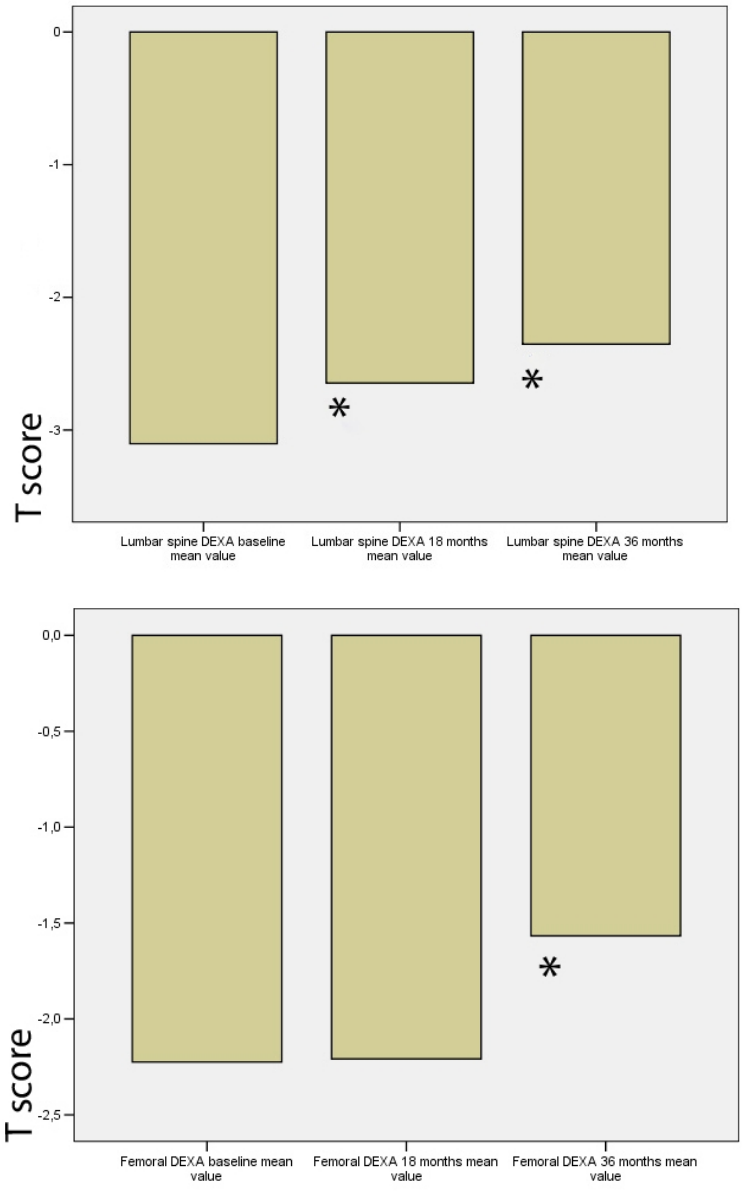

Fig. 1. Mean and 95% C.I. values of T-score in i) lumbar spine and ii) femur, measured by dual-energy X-ray absorptiometry at baseline, after 18 months of neridronate 100 mg administered IV every 2 months, and after a subsequent 18-month period during which neridronate (25 mg every month) was administered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

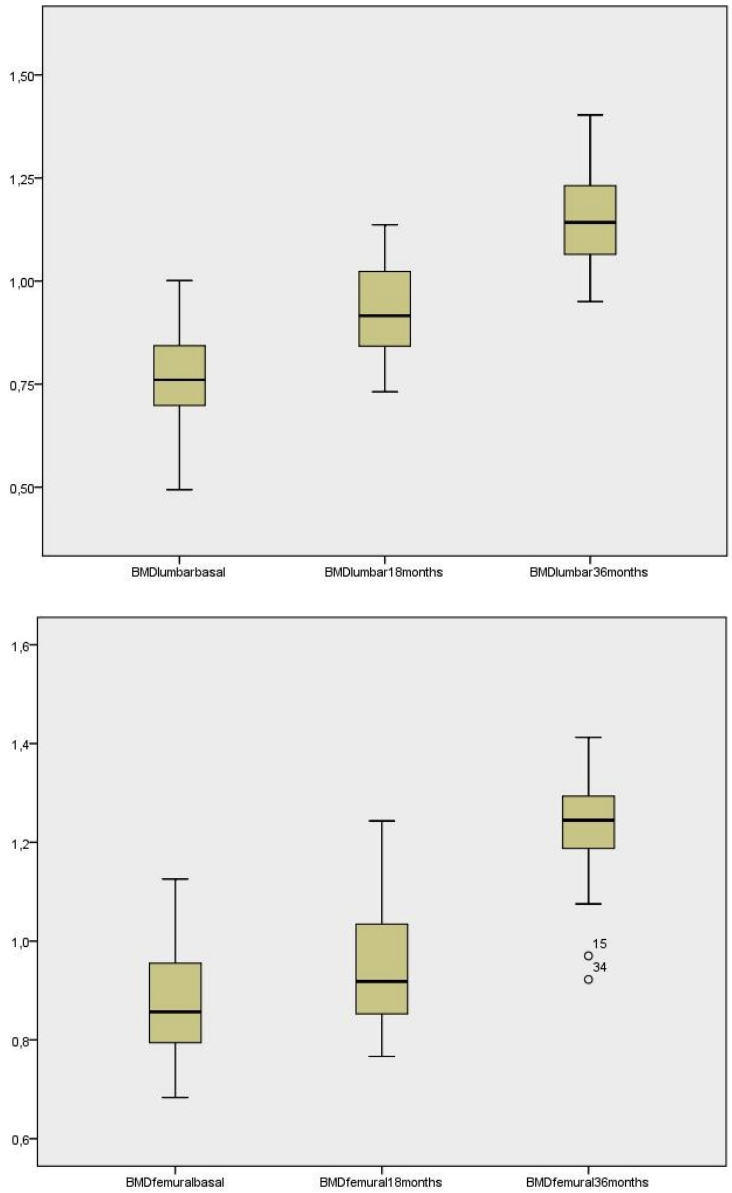

Fig. 2. Mean and 95% C.I. values of absolute bone density (g/cm^2) in i) lumbar spine and ii) femur

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 and T-score values with respect to baseline both at 18 and at 36 months, suggest that this administration regimen for NER may increase BMD and conversely reduce FRAX index 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.

4. CONCLUSION

In conclusion, this study provides further 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.

COMPETING INTERESTS

No conflicts of interest are present for all the authors of the manuscript.

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