Original article

Intramuscular neridronate in patients with rheumatoid arthritis using corticosteroids: evaluation of treatment adherence in a randomized, open-label comparison with other bisphosphonates

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Abstract. *Background and aims:* Oral bisphosphonates have been used successfully in patients with rheumatoid arthritis (RA), but their use for the treatment of corticosteroid induced osteoporosis may be limited by poor compliance. Neridronate, an intramuscular and intravenous aminobisphosphonate approved for the treatment of osteogenesis imperfecta and Paget's disease, is also effective in postmenopausal osteoporosis. The aim of this study was to compare the adherence of intramuscular neridronate versus oral alendronate or risedronate in patients with RA with corticosteroid-induced osteopenia. *Methods:* This randomised, open label, parallel-group, single centre study enrolled post-menopausal women (50–70 years), with RA and osteopenia (T-score >–2.5) who were receiving stable dose of methylprednisolone 5 mg or equivalent within the previous 3 months, and expected to continue therapy for at least 12 months. Patients were treated with intramuscular neridronate 25 mg administered once a month, or oral alendronate 70 mg or oral risedronate 35 mg both administered once-weekly, for 12 months. The main outcome measure was adherence to treatment over 1 year, assessed using the Morisky Medication Adherence Scale 4-item (MMAS-4; adherence defined as patients with MMAS-4 score ≥3). *Results:* Of 87 women (mean age 61.5 ± 9.2 years) enrolled, 30 were randomized to neridronate, 27 to alendronate and 30 to risedronate therapy. Adherence rates after 12 months were significantly higher with neridronate than with alendronate or risedronate (76.7% vs 47.8% and 48.0%; $p<0.05$ for both versus neridronate). After 12 months, lumbar and femoral neck BMD and DAS28 were significantly improved in all groups compared with baseline ($p<0.05$) with no significant difference between the three treatment groups. *Conclusion:* Neridronate is associated with significantly improved adherence to therapy compared with alendronate and risedronate, and improves BMD and disease activity in postmenopausal women with RA and osteopenia. Intramuscular monthly neridronate represents a convenient treatment option for patients with RA using corticosteroids.. (www.actabiomedica.it)

Key words: adherence, efficacy, neridronate, alendronate, risedronate, intramuscular, oral

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease associated with an increased risk of osteoporosis, and characterised by bone loss and fracture (1-3). In Italy, the prevalence of osteoporosis in women with RA ranges from 30 to 40%, depending on which sites are assessed by densitometry (4). Furthermore, the prevalence of bone disease in RA can reach 80%, if less severe conditions, such as osteopenia, are considered (5).

The aetiopathogenesis of osteoporosis in RA is multifactorial and includes immobility due to pain and loss of joint function (6, 7), the action of inflammatory cytokines (8, 9), and the osteopenic effect of

most disease modifying antirheumatic drugs (DMARDs) (8, 9). Corticosteroids, effective therapies that are widely used for the treatment of chronic inflammatory arthropathies, play an important role in the development of osteoporosis in patients with RA (4, 10). However, chronic use of these agents can lead to the early and rapid loss of bone mineral density (BMD) in the trabecular bone of lumbar vertebrae and ribs, and an increase in the risk of fractures (3, 10, 11).

Several national guidelines on the prevention and treatment of corticosteroid-induced osteoporosis highlight the importance of primary prevention in high-risk patients who are beginning corticosteroid therapy, the use of bisphosphonates as a front-line therapeutic option, and the role of calcium and vitamin D supplementation (12-18).

Bisphosphonates are currently the preferred drugs for the treatment of corticosteroid-induced osteoporosis and evidence supporting their use comes from several clinical trials investigating their effect on BMD and reduction of the risk of fractures (19-22). However, while oral bisphosphonates, such as alendronate and risedronate, have been successfully used in patients with RA, their use for the treatment of osteoporosis has been limited by the frequently reported poor compliance to therapy (23-25).

Therefore, over the years it has become increasingly important to develop not only new therapies for the prevention and treatment of osteoporosis and osteoporotic fractures, but also to find therapies which have a better compliance rate. To improve compliance with osteoporosis therapy, bisphosphonates with alternative administration routes (intravenous or intramuscular), longer intervals between doses, and a reduced risk of gastrointestinal side effects have been developed.

Neridronate is an aminobisphosphonate, which is approved in Italy for the treatment of osteogenesis imperfecta and Paget's disease (26-30). It is available in 25 mg and 100 mg doses for intramuscular and intravenous administration.

Neridronate has been also been shown to be effective for the treatment of postmenopausal osteoporosis (27, 31, 32) and to inhibit bone resorption in active RA (33, 34).

This study was conducted to compare the adherence to intramuscular neridronate with adherence to oral administration of alendronate or risedronate in patients with RA and corticosteroid-induced osteopenia. Efficacy and tolerability were also assessed.

Patients and methods

Study Setting and Design

This randomised, open label, parallel-group study was carried out at the Unit of Rheumatology, Hospital "A. Galateo", Lecce, Italy from 2007 to 2010. The study protocol was approved by the local ethics committee and performed according to the Helsinki Declaration. Written informed consent was obtained from all patients before their enrolment in the study.

Eligibility Criteria

Postmenopausal women, aged 50 to 70, with RA diagnosed according ACR (American College of Rheumatology) criteria and osteopenia (T-score >-2,5 SD) were enrolled.

In the study were included only patients who had started treatment with stable dose of 5 mg of methylprednisolone, or its equivalent, within the previous 3 months, and were expected to continue the therapy for at least 12 months.

Exclusion criteria included the presence of concomitant metabolic bone disease (postmenopausal or glucocorticoid-induced osteoporosis), concomitant treatment with other compounds affecting bone metabolism, severe renal impairment (serum creatinine >1.3 mg/dL), major gastrointestinal disorders, presence of other clinically significant diseases and a history of intolerance to oral bisphosphonate treatment.

Interventions

Women were randomised to 12 months' therapy with intramuscular neridronate 25 mg administered once a month, oral alendronate 70 mg or oral risedronate 35 mg, both administered once-weekly. Daily oral supplementation with vitamin D_3 (800 IU) and

calcium (1 g) were administered over the study period. Patients also received methotrexate 10–15 mg weekly, non-steroidal anti-inflammatory drugs and proton pump inhibitors.

Endpoints

The primary endpoint was adherence to treatment over 1 year. This was assessed using the Morisky Medication Adherence Scale 4-item (MMAS-4). This simple, validated 4-question survey assessed the likelihood that patients take their medications as prescribed. The questions were as follows: Do you ever forget to take your medicine? Are you careless at times about taking your medicine? When you feel better do you sometimes stop taking your medicine? Sometimes if you feel worse when you take the medicine, do you stop taking it? To score the questionnaire, each "yes" response is given a score of 0, and each "no" response is given a score of 1 (range 0 to 4). According to the Morisky classification, adherence is divided into 3 groups: high for those scoring 3 or 4, medium for those scoring 1 or 2, and low for those scoring 0, when scoring one point for each "yes" answer (35). In this study, for each patient "adherence" was defined as an MMAS-4 score of at least 3.

The secondary endpoints included lumbar and femoral neck BMD which was evaluated with dual-energy X-ray absorptiometry (DXA) [QDR®; Hologic] at baseline and after 12 months and the 28-joint Disease Activity Score (DAS28) which was measured every three months.

Statistical Analysis

The primary endpoint, the number and percentage of patients showing "adherence" to the treatment, evaluated with MMAS-4, was analysed by means of chi-square test. The MMAS-4 score was described. Secondary endpoints were analysed as follows: BMD, recorded as the percent change from baseline at 12 months, was analysed with ANOVA; furthermore the change from baseline was analysed by the means of Wilcoxon test for paired samples; DAS28, was measured at baseline and at months 3, 6, 9 and 12, by means of repeated measures ANOVA. Statistical significance was defined as a p-value of <0.05.

Results

Patients

Eighty seven women (mean age 61.5 ± 9.2 years) were enrolled in the study and randomly allocated to the three treatment groups (30 to neridronate, 27 to alendronate and 30 to risedronate). All patients where RF+ and 7 patients where anti-CCP+. Baseline demographic and clinical characteristics of patients were similar between the patient groups (Table 1). Four and five patients in the alendronate and risedronate groups, respectively, withdrew from the study due to adverse events.

Table 1. Patient demographics and characteristics. Data are mean ± SD*

	Neridronate (n = 30)	Alendronate (n = 27)	Risedronate (n = 30)
Age, years	62.5±9.4	59.0±9.0	62.8±8.9
Height, cm	155.3±6.5	157.6±5.8	155.0±6.1
Weight, kg	58.7±8.4	61.4±10.3	61.3±8.9
Lumbar BMD‡, g/cm^2	0.821±0.152	0.827±0.219	0.864±0.223
Femoral Neck BMD, g/cm^2	0.659±0.151	0.685±0.142	0.687±0.174
Patients with at least 1 vertebral fracture (%)	3,3	3,7	3,3
Duration of AR disease (years)	6,3±3,2	5,9±3,1	6,2±3,6
Steroid in the last 2 years# (mg/die)	5,7±1,4	5,6±1,4	5,8±1,5
Methotrexate in the last 2 years (mg per week)	12,2±3,3	12,5±3,6	12,6±3,7
DAS28†	5.4±1.8	5.6±1.9	5.3±1.7

*Standard Deviation; †28-joint Disease Activity Score; ‡Bone Mineral Density; #Methylprednisolone or equivalent

Table 2. Adherence to therapy during the 12-month study assessed using the Morisky Medication Adherence Scale-4 item (MMAS-4)

	Neridronate	Alendronate	Risedronate
	(n = 30)	(n = 23)	(n = 25)
Patients reported to be adherent to treatment[a], n (%) (95% CI)	23 (76.7) (61.5 - 91.8)	11 (47.8)[b] (27.4 - 68.2)	12 (48.0)[c] (28.4 - 67.6)
Mean MMAS-4 score (95% CI)	3.10 (2.73 - 3.47)	2.78 (2.35 - 3.21)	2.68 (2.27 - 3.09)

[a] Adherence was defined as a score of at least 3 on the MMAS-4 scale
[b] $p < 0.03$ vs neridronate
[c] $p < 0.02$ vs neridronate

Table 3. Mean percent change from baseline in bone mineral density (BMD) at month 12. Data are mean ± SD*

	Neridronate (n = 30)	Alendronate (n = 23)	Risedronate (n = 25)
Lumbar BMD	3.12 ± 3.32†	3.01 ± 3.48†	2.92 ± 3.27†
Femoral Neck BMD	1.63 ± 3.62†	1.61 ± 3.54†	1.58 ± 3.67†

*Standard deviation; †$p<0.05$ vs baseline

Adherence Evaluation (MMAS-4)

The numbers and proportions of patients adherent to therapy for the three treatments after 12 months are shown in Table 2. The adherence rate for neridronate was significantly higher than those for alendronate or risedronate ($p < 0.03$ for alendronate vs neridronate and $p<0.02$ for risedronate vs neridronate).

Change in BMD and Disease Activity (DAS28)

After 12 months, lumbar and femoral neck BMD was significantly increased in all treatment groups compared with baseline ($p<0.05$) with no significant difference among the three treatment groups (Table 3 and Figure 1).

The DAS28 was significantly reduced from baseline ($p<0.05$) to a similar extent in all bisphosphonate groups after 12 months with no significant difference between the three treatment groups (Figure 2).

Safety Evaluation

Neridronate was well tolerated. No patients receiving neridronate discontinued therapy due to an

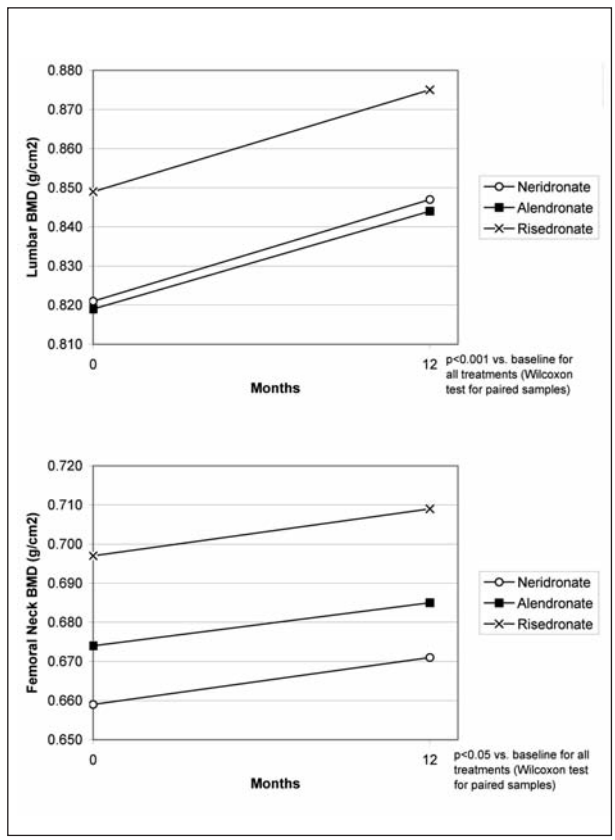

Figure 1. BMD values during the 12 month

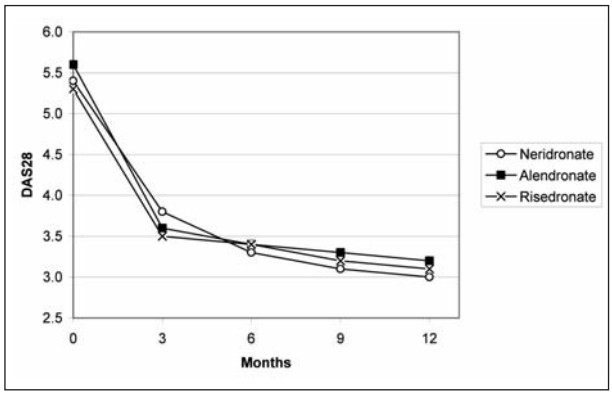

Figure 2. Change from baseline in the 28-joint Disease Activity Score (DAS28) from baseline to month 12 with neridronate, alendronate or risedronate treatment in patients with RA.

adverse event. In comparison, four patients in the alendronate group (14.8%) and five patients in the risedronate group (16.6%) discontinued therapy due to gastro-oesophageal adverse events. One patient (3.3%) receiving neridronate showed a flu-like reaction with 48-hour hyperpyrexia after the first dose and three patients (10%) receiving neridronate experienced temporary pain at the injection site.

Discussion

Our study demonstrated that long-term, once-monthly administration of intramuscular neridronate 25 mg was associated with significantly higher adherence rates than once-weekly oral alendronate 70 mg or risedronate 35 mg in women with osteopenia and RA. Neridronate had a positive effect on BMD in RA, which was similar to that observed with alendronate and risedronate. Moreover, neridronate was associated with a similar improvement in DAS28 scores to alendronate and risedronate, confirming the potential anti-inflammatory action of bisphosphonates, which has been previously described (33). The efficacy observed with neridronate was similar to that observed with the other oral bisphosphonates (alendronate, risedronate) that were also investigated in this study. However, intramuscular neridronate appears to have an advantage as it was associated with a significantly higher adherence rate than alendronate and risedronate. There are several reasons for the lower adherence to therapy with oral bisphosphonates. They have a low bioavailability (36, 37) and are associated with a high frequency of gastrointestinal events (especially esophagitis) (25, 38, 39). Sometimes, oral bisphosphonates may be difficult to administer; in fact, they require a large amount of water for tablet intake and an upright position is recommended for 30–60 minutes after administration (40). Often oral bisphosphonates are administrated with other drugs and they must be taken on an empty stomach, at least half an hour or one hour before breakfast which can be difficult for some patients (41).

To improve adherence with osteoporosis therapy, bisphosphonates with alternative administration routes (intravenous or intramuscular), with longer intervals between administrations, and with a reduced risk of gastrointestinal side effects have been developed. Neridronate is one such bisphosphonates. The results of this study highlight that neridronate, with an intramuscular dose administered once per month, was associated with better adherence than oral once-weekly alendronate or risedronate in patient with RA and osteopenia.

This higher adherence rate with intramuscular administration of neridronate is particularly interesting. This, in a clinical setting, may lead to a decrease in the number of oral drugs required in patients who require polytherapy and could consequently reduce the risks associated with gastric intolerance in patients with co-morbid conditions receiving bisphosphonate therapy.

Our results are similar to those reported in other studies of intramuscular administration of bisphosphonates. Clodronate, with its intramuscular administration, has been the most frequently used bisphosphonate for the treatment of osteoporosis since its approval and has been associated with a good adherence (42-44).

Treatment with bisphosphonates in patients receiving corticosteroids is particularly interesting from a pharmacoeconomic point of view. They have been shown to be potentially useful and cost-effective, particularly in patients with higher risk of fracture (45). Based on this we recommend that prophylactic treatment with bisphosphonates should be prescribed, re-

gardless of bone mass, if treatment with corticosteroids is going to last for more than 3 months.

Limitations of the study include the bias in the gender of the population considered, as only women were enrolled. Further studies with male patients would be required in order to draw conclusions on the effects of the treatment on the male population. Another limitation is the open label design of the study. However, a double dummy design would have impacted negatively on the evaluation of the adherence.

Conclusion

Our study shows that neridronate improves BMD, decreases disease activity and is associated with significantly improved adherence to therapy, compared with alendronate and risedronate in postmenopausal women with osteopenia and RA. Monthly administration of 25 mg intramuscular neridronate represents a convenient alternative for patients with RA using corticosteroids which may facilitate improved prevention and treatment of osteoporosis in this patient sub-group.

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