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Bone Density, Bone Turnover and Fracture Risk in Ankylosing Spondylitis: A Randomized Placebo-Controlled Trial of Oral Alendronate

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Abstract

Objectives: The aim of this multicentre study was to determine the effect of oral alendronate over 2 years on Bone Mineral Density (BMD) and bone turnover in patients with Ankylosing Spondylitis (AS).

Methods: 180 patients were randomised to receive alendronate 70 mg weekly or placebo. Change in BMD over 2 years was assessed by Dual X-Ray Absorptiometry (DXA) scan, bone turnover by serum markers (Procollagen Type 1 Amino-Terminal Propeptide (P1NP) and Carboxy-Terminal Collagen Crosslinks (CTX)) and vertebral fracture by bone morphometry.

Results: At 2 years, patients in the alendronate group showed a significant mean increase in BMD of 5.6% at the lumbar spine compared to a mean increase of 1.4% in the placebo group. At all regions of the hip, BMD increased significantly in the alendronate group. There was a non significant decrease at all hip site in the placebo group. Serum markers showed a significant ($p<0.001$) reduction in bone turnover in the treated group but not in the placebo. No incident morphometric vertebral fracture rates were observed in either group.

Conclusions: Oral alendronate is effective at reducing bone turnover and increasing BMD in patients with established AS. Although not demonstrable in this short study, an effect on fracture risk is likely to be seen in a higher risk group treated over a longer period.

Introduction

Bone Mineral Density (BMD) is reduced in Ankylosing Spondylitis (AS) even in the early phase of the disease [1,2]. The degree of reported bone loss is variable, reflecting different study populations and disease durations, and the different techniques used to measure BMD. The reasons for this low BMD are multifactorial and may include inflammation associated with disease activity, immobility, vitamin D status, medication and altered sex hormone levels [3-6]. Reduced BMD is associated with an increased vertebral fracture rate in patients with AS compared to age and sex matched populations; these fractures may cause significant morbidity [4,7,8]. Vertebral fractures in AS may exacerbate spinal deformity, may present with acute pain, and in some cases neurological deficit [4,7-10]. It has also been suggested that microfractures occurring as a result of reduced bone mass may exacerbate pain and worsen deformity [1]. Bisphosphonates are potent inhibitors of bone resorption, acting by inhibiting osteoclast activity via inhibition of the enzyme farnesyl diphosphate synthase in the mevalonate pathway. In women and older men they improve BMD and in women have been proven to reduce vertebral, hip and other fractures. Preserving BMD in patients with AS may lead to a reduction in fractures, vertebral deformity and pain. A rise in BMD with an intravenous bisphosphonate (neridronate) was reported in a small (n= 30) open label study [11] but there is currently no consensus regarding treatment of low BMD in patients with AS and, notably, no information on the effect of more widely used oral bisphosphonates. We performed a two-year double blind randomized controlled trial to assess the clinical efficacy of alendronate,

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an oral bisphosphonate, in AS. We found no beneficial effect on any AS specific clinical outcome [12]. This paper presents the results of further analysis of the study to determine whether an oral bisphosphonate commonly used for the treatment of osteoporosis in other populations has a similar beneficial effect on BMD and fracture risk in AS.

Materials and Methods

The study was a double blind, randomized placebo-controlled trial with patients receiving either alendronate 70 mg weekly or placebo over 2 years. Inclusion and exclusion criteria have been previously reported [12]. Osteoporosis related exclusion criteria included: any disease process that might affect BMD (e.g. inflammatory bowel disease, osteomalacia, and hyperparathyroidism), glucocorticoid use within 3 months (2 months for intra-articular injection), and previous exposure to bisphosphonate or contraindications to bisphosphonate use, and previous surgery that would prevent accurate BMD measurement by DXA. Patients with more than two low trauma fractures were excluded as it was felt unethical to subject these patients to the risk of being in the placebo arm of treatment.

Six UK centres participated. Patients were invited to participate from rheumatology outpatients or local National Ankylosing Spondylitis Society (NASS) groups with letters of invitation being sent to patients who had given permission to be contacted through the NASS database. Each patient received an information sheet explaining the study and a consent form. Written informed consent was obtained from all patients. Ethical approval was received from Trent MREC and site specific approval was obtained for the 6 UK recruiting centres. The study was undertaken in accordance with the ethical standards of the responsible committee and with the Helsinki Declaration of 1975, as revised in 1983.

At baseline, all patients completed a socio-demographic questionnaire including disease duration, age, gender, height, weight and smoking status. Clinical measures and C - reactive protein (CRP) were recorded at baseline and throughout the study. Clinical outcomes are reported elsewhere [12].

Serum for measurement of bone markers was taken at baseline and 12 months. Samples (3 mls into EDTA containing tube) were taken in the morning (900-1000) after an overnight fast and stored at -70°C to be measured in a single batch for all time points. P1NP, a marker predominantly of bone formation and CTX, a marker primarily reflecting bone resorption, were measured. Assays used were the Elecsys P1NP assay and Elecsys β-CrossLaps/serum assay (Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim).

BMD was measured by dual X-ray absorptiometry (DXA) at baseline and 24 (+/-1) months. Four centres used Hologic equipment and two used GE Lunar. Standard conversion formulae [13,14] were used to allow comparison between machines and subsequent changes were measured using standardized values. Subjects were classified at baseline using standard WHO criteria into normal (T score > -1.0); osteopenia (T score -1.0 to -2.5) or osteoporosis (T score ≤ - 2.5).

X-rays (lateral cervical spine, lateral thoracic spine, lateral lumbar spine, AP lumbar spine, and pelvis) were performed at 0 and 24 months. Vertebral fractures were assessed on thoracic and lumbar spine radiographs at baseline and 24 months using the algorithm-based qualitative (ABQ) method at a single centre [15,16]. Radiographic severity of AS was measured using two AS-specific composite indices characterizing radiologic changes in the spine: the Bath AS Radiographic Index (BASRI) and the Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). Baseline BASRI was available on 84/88 patients treated with alendronate and 82/92 patients on placebo; Baseline mSASSS on 76/88 patients treated with alendronate and 73/92 patients on placebo. X-rays were read by 2 observers blinded to treatment arm or placebo. We did not document how many patients developed new syndesmophytes. Safety data was recorded at each visit.

Analysis was performed on an "intention to treat" principle using SPSS version 16 (IBM). Baseline characteristics are summarised by randomised group.

Results

180 patients were randomized, 88 to alendronate and 92 to placebo. Table1 summarizes the baseline characteristics of both groups. About 80% subjects were male, with a mean age of 47 years and mean disease duration of 20 years.

There were no significant differences between treatment groups in demographic features, CRP, AS clinical severity, or radiographic severity as measured by BASRI or mSASSS. There were more "current" smokers in the alendronate group and more "never" smokers in the placebo group but these differences were not significant (p=0.064).

Baseline values for bone turnover markers and BMD are shown in Table 1 and did not differ between groups. At baseline, 11 morphometric vertebral fractures were seen in 9/88 patients in the alendronate group (2 subjects in this group had 2 fractures) with 7 fractures in 7/92 subjects receiving placebo. There was no difference in BMD at any site between the 16 subjects with baseline fractures and those without.

Follow-up, reported in accordance with CONSORT recommendations, has been published previously [12]. In summary, one patient on placebo was lost to follow up. 29 patients discontinued treatment (14 receiving alendronate and 15 receiving placebo). All patients completing the study complied with the protocol requirement that patients take at least 70% of the study medication (according to recorded tablet counts).

Results are presented in Table 2. In the treated group, P1NP fell by 20 ng/ml from a mean value of 37.6 ng/ml at baseline to 17.6 ng/ml at 12 months; a mean fall of 53%. CTX fell by 0.20 µg/L from a mean of 0.36 µg/L to 0.16 µg/L; a mean fall of 55%. No fall was seen in the placebo groups and the difference between reduction in active and placebo groups was significant (p <0.001).

BMD results are presented for hip (femoral neck, trochanteric and total hip) and lumbar spine. Results are expressed as the percentage change in absolute BMD (g/cm^2). There was an improvement in absolute BMD (g/cm^2) at all sites in the alendronate group with a rise of 1.8-5.6% depending on site. In the placebo group there was a non-significant increase of 1.36% in BMD at the lumbar spine and a non-significant decrease at all three hip sites (-0.06 - -0.25 %). Differences between groups were statistically significant.

Due to missing measurements on individual scores, or failure to have follow-up radiographs, it was only possible to compare baseline

Table 1: Disease measures at baseline. All differences are between groups and non significant (p>0.05).

	Alendronate (n = 88)		Placebo (n = 92)	
	Mean	**SD**	**Mean**	**SD**
Males	74 (84%)		74 (80%)	
Age (yrs)	47.1	11.6	47.4	12.3
BMI	28.5	6.1	27.8	5.0
Smoking Status:				
Never	30		45	
Ever	29		29	
Current	29		18	
Disease duration (yrs)	19.7	10.7	20.8	12.7
BAS-G (0-10)	4.3	2.3	4.2	2.3
BASDAI (0-10)	4.2	2.4	4.1	2.1
BASFI (0-10)	3.8	2.5	3.6	2.2
BASMI (0-10)	2.7	1.0	2.9	1.1
CRP(mg/l)	14.2	17.2	11.2	11.8
BASRI[a] (0-16)	9.37	2.34	9.91	2.76
mSASSS[b] (0-72)	20.88	18.25	25.07	21.05
P1NP (ng/ml)	37.58	15.56	40.21	17.56
CTX (µg/L)	0.36	0.2	0.37	0.23
T score:				
Lumbar spine	-0.32	1.19	0.039	1.85
Total hip	-0.22	0.87	-0.28	1.09
Intertrochanteric	-0.12	0.92	-0.20	1.05
Neck of femur	0.68	1.04	-0.85	1.05
BMD group:				
Normal	41 (47%)		35 (39%)	
Osteopenia	41 (47%)		44 (49%)	
Osteoporosis	6 (7%)		10 (11%)	
Morphometric vertebral fractures	11		7	

Table 2: Change in CRP, bone turnover markers and BMD (over 24 months unless stated).

Variable	Alendronate	Placebo	P value
CRP (mg/L)	-7.72	-2.58	0.178
P1NP (ng/ml)[a]	-20.00	-1.34	<0.001
CTX (µg/L)[a]	-0.20	-0.03	<0.001
Lumbar spine BMD % change	5.58 (± 4.54)	1.36 (± 4.30)	<0.001
Total hip BMD % change	2.86 (± 3.11)	-0.12 (± 3.25)	0.009
Intertrochanteric BMD % change	3.64 (± 3.90)	-0.06 (± 4.40)	<0.001
Neck of femur BMD % change	1.76 (± 4.64)	-0.25 (± 4.54)	<0.001

[a]Change over initial 12 months. In the alendronate group a fall of 53% was seen for P1NP, fall of 55% for CTX.

and final visit mSASS in 58/88 in the alendronate group and 57/92 in placebo. In the alendronate group baseline mSASSS was 17.54 (± 16.50); at 2 years score was 17.72 (± 17.39). In the placebo group baseline mSASSS was 24.29 (± 20.59); at 2 years score was 24.76 (± 21.27). There was no significant difference between the groups at baseline or at final visit. The mean increase in mSASSS for alendronate was 0.18, for placebo 0.47 (p=0.8). We could not therefore detect a difference in the development of new syndesmophytes. No incident vertebral fractures were observed in either group during the course of the study.

158 (87%) patients were on concomitant NSAIDs at baseline (84 receiving alendronate and 74 placebo) but there was no increased occurrence of upper gastrointestinal side effects. 17/88 patients taking alendronate reported upper GI side effects (reflux, nausea, upper abdominal pain etc.) of whom 5 were not taking NSAIDs (10/17 recorded as taking NSAIDs, 5/17 not taking NSAIDs, 2/17 not recorded) compared to 11/92 patients on placebo. There was one upper GI serious adverse event, a duodenal ulcer which occurred in a subject taking placebo. There were no reports of osteonecrosis of the jaw or atypical fractures. Secondary analysis of protocol completers showed no significant differences from the primary ITT analysis.

Discussion

This study demonstrates that oral alendronate is effective at significantly improving BMD at femoral neck, intertrochanteric region, total hip and lumbar spine in patients with AS. Bone turnover is also reduced, with a fall in turnover markers of about 50%. This reduction is broadly similar with that seen in other populations and indicates a bisphosphonate effect on osteoclasts [17].

Over a two year period the expected population trend would be a slight decrease in BMD at all sites. In the placebo group there was a small, non - significant fall in BMD at femoral neck, trochanteric and total hip; in the treated group a rise was seen at these sites. At lumbar spine BMD improved in both groups, though the rise was significantly greater in the alendronate group. The small increase in spine BMD in the placebo group may reflect syndesmophyte formation (although we were unable to detect that in this study). It has long been recognised that syndesmophytes, as well as disc degeneration and osteophyte formation at the lumbar spine, can result in falsely high BMD estimation due to presence of extra bone. For this reason, the hip is the preferred site for studies of BMD in AS because it avoids these confounding factors. It is theoretically possible that the rise in BMD in the alendronate group also reflects syndesmophyte formation. However, the magnitude of the rise was significantly greater than in the placebo group despite the fact that mSASSS score (dependent on syndesmophyte formation) did not increase more in the alendronate group (if anything the increase was less than in the placebo group). The observed increase in BMD in the alendronate group is, therefore, likely to be a true reflection of bone mass rather than an artefact due to syndesmophytes. Indeed, alendronate has been shown to reduce osteophyte formation in studies of patients with osteoporosis [18] and a similar effect on syndesmophytes cannot be excluded.

In both sexes BMD is a risk factor for fracture and is widely used as a surrogate marker for fracture risk [19]. We may have expected, therefore, that the observed improvement in BMD would be associated with a reduction in incidence of fractures. However,

over 24 months, we were unable to detect a difference: indeed no new radiographic vertebral fractures were seen in either group (height, a surrogate measure of fracture, could not be used as AS is characterized by progressive kyphosis: any change in height may therefore reflect disease progression rather than presence or absence of vertebral fracture). Maas et al. [20] reported that 6% patients (n = 292, some of whom were taking steroids) developed vertebral fractures over 2 years: patient age was similar to this study but baseline prevalence of vertebral fractures was much higher at 26%. 10% of their subjects also had inflammatory bowel disease, 28% uveitis and 11% with psoriasis. Kang et al. [21] had a similar baseline prevalence of vertebral fracture (10.8%) but an incidence of 4.7% at 2 years. Again they differ from our group as some were taking methotrexate and few were on bisphosphonates. It is likely that the low incident fracture rate in our study, compared with other reports, in part reflects difference in patient populations.

In addition, it is relevant that patients in this study had a higher baseline BMD than that seen in studies of Post-Menopausal Osteoporosis (PMO), and even that seen in other studies of AS [3,22]. They therefore reflect a relatively low risk population for fracture, reducing the chance of demonstrating a reduction in number of fractures. It is probable that the higher baseline BMD in this cohort reflects the fact that patients at high risk of fracture, as well as those with conditions known to effect bone metabolism, were excluded because this was an interventional rather than an observational study. The mean baseline BASDAI for this cohort is consistent with moderate disease activity, as would be expected in routine clinical practice in secondary care. The low incidence of morphometric vertebral fractures cannot therefore be explained by low disease activity.

Previous studies of BMD in AS have recruited from tertiary referral centers with more active disease and consequently lower BMD and higher risk of fracture. Numbers of vertebral fractures recorded at baseline were similar to those recorded in some previous studies [8] though others, as indicated above, report higher prevalence [20].

Finally it may be that the risk factors for spinal fracture in AS differ from those in PMO and the influence of BMD may be relatively less. Bone quality, for example, may differ between these two conditions. It is possible that a study of longer duration than 2 years may be able to demonstrate a reduction in fractures.

Alendronate was also found to be safe in this cohort with no significant serious adverse events or greater gastrointestinal toxicity in this group despite taking concomitant regular NSAIDs.

This study recruited patients from general rheumatology departments, rather than tertiary referral centers, and the results are therefore likely to be more generalizable to standard hospital outpatients than previous studies recruiting patients from tertiary centers.

In summary, this is the first study to show that the oral anti-resorptive drug alendronate improves BMD and suppresses bone resorption in AS, significantly more effectively than placebo. The drug was safe and well tolerated. This suggests a potential role for alendronate in reducing fracture risk in those patients with AS who are at a high risk of fracture.

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