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Authors

Host, LV
Keen, HI
Laslett, LL
et al.

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Zoledronic acid does not slow spinal radiographic progression of osteoarthritis in postmenopausal women with osteoporosis and radiographic osteoarthritis

L.V. Host, H.I. Keen, L.L. Laslett, D.M. Black and G. Jones

Abstract

Introduction: *Post hoc* analyses of osteoporosis trials have suggested that alendronate and strontium ranelate may be associated with a reduction in the progression of spinal radiographic osteoarthritis (OA). We performed an analysis on a subgroup of participants in the horizon PFT trial (a 3-year randomized controlled trial (RCT) of yearly zoledronic acid (ZA) in postmenopausal women with osteoporosis), to evaluate the effect of ZA on the structural progression of spinal osteophytes (OPh) and disk space narrowing (DN).

Methods: Paired lateral spinal X-rays (baseline and 36 months) were selected from the horizon PFT trial records restricted to those with radiographic OA at baseline. The X-rays were analyzed by two readers blinded to the treatment allocation. OPh and DN were scored separately using the Lane atlas (0–3 for increasing severity at each vertebral level) at all evaluable levels from T4–12 and L1–5.

Results: A total of 504 sets of paired radiographs were included in the analysis, 245 in the ZA group and 259 in the placebo group. Overall, the rates of change of OPh and DN scores were low, and they were not statistically different between the groups (change in the whole spine OPh ZA 1.0 ± 1.6, placebo 0.8 ± 1.3, $p = 0.1$; DN ZA 0.3 ± 1.0, placebo 0.3 ± 0.8, $p = 0.7$).

Conclusion: Yearly ZA for 3 years was not associated with a slowing of progression of OPh or DN in the thoracolumbar spine in patients with pre-existing radiographic OA.

Keywords: bisphosphonates, spinal osteoarthritis, treatment, zoledronic acid

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Correspondence to:
H.I. Keen
Rheumatology Department, Fiona Stanley Hospital, Murdoch, WA, Australia

School of Medicine, University of Western Australia, Perkins South Building, FSH, Murdoch Drive, Murdoch, WA 6150, Australia
Helen.keen@uwa.edu.au

L.V. Host
Rheumatology Department, Fiona Stanley Hospital, Murdoch, WA, Australia

L.L. Laslett
G. Jones
Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia

D.M. Black
Division of Clinical Trials & Multicenter Studies, University of California, San Francisco, CA, USA

Introduction

Osteoarthritis (OA) is the most common chronic joint disorder,[1] and it can affect any diarthrodial joint, but most frequently manifests in the knee, hip, spine, and hand.[2] Despite its prevalence and association with significant disability, current pharmacotherapy choice for OA is quite limited, and analgesic agents have moderate efficacy and raise some safety concerns.

Novel imaging studies have revealed that OA is a disease of the whole organ, and it is associated with osteophytes (OPh), synovial inflammation, and subchondral bone changes. In the past, however, OA was thought to be primarily a disease of cartilage. It is now recognized that aberrant bone remodeling results in sclerosis of the subchondral plate, osteophyte formation, and thickening of the calcified layer of cartilage. Moreover, mechanical stress leads to formation of microfractures, cysts, and bone marrow lesions.[3,4] Activated osteoblasts produce inflammatory cytokines and angiogenic factors, triggering activation of chondrocytes and osteoclasts. The common endpoint of these processes is subchondral bone remodeling and activation of pain pathways that characterize OA.[5] Bisphosphonates have been shown to inhibit osteoclast activity, limit

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bone remodeling, and may suppress the associated pain.[6,7] Therefore, they may have both analgesic efficacy and structure-modifying effects,[8] particularly in early OA.

Evidence from animal models suggests that anti-resorptive therapy may slow the structural progression of OA.[9,10] In humans, randomized controlled trial (RCT) studies have focused on the knee (as it is the most feasible joint to study) and have yielded conflicting results regarding the analgesic and structure-modifying effects of oral bisphosphonates.[7,11–16] It is important to note that OA is a heterogeneous disorder with shared pathological features; hence, evidence from the knee studies may not be applicable to the spine. Spinal OA, as a primary cause of low back pain, is an important health concern to study. Low back pain is a common condition associated with high economic costs and significant healthcare burden.[17] The literature on the effects of bisphosphonates on OA largely focuses on the knee, with little evidence regarding the spine. However, some data suggest that bisphosphonates may have analgesic efficacy in spinal OA. Zoledronic acid (ZA), a yearly intravenous (IV) bisphosphonate studied in the horizon pivotal fracture trial (PFT) and compared to placebo, was associated with a statistically significant reduction in the number of days with back pain and number of days with limited activity due to back pain in postmenopausal women with osteoporosis.[18] This benefit was independent of changes in bone mass and fractures, highlighting the possibility that its analgesic efficacy may be mediated by OA modification[18] or Modic changes[19] (Modic changes are spinal degenerative lesions visible as bone marrow lesions and vertebral endplate lesions on magnetic resonance imaging (MRI)[20]). However, ZA did not demonstrate an effect on Modic changes per se, and the effects of ZA on radiographic structure in OA have not been investigated.

The effects of other bisphosphonates on structural progression of spinal OA have been investigated. A small *post hoc* analysis of a pivotal study of alendronate in spinal osteoporosis demonstrated a small but significant reduction in progression of radiographically detected spinal OA, indicating that bisphosphonates may have disease-modifying effects in OA.[21] Given that previous findings suggest that ZA may have an analgesic efficacy[18] and that alendronate may have structural effects,[21] it is of scientific interest to determine whether ZA has any structural effects in spinal OA, which could be supportive of a clinical role for anti-resorptive agents in this common condition. Therefore, the aim of this study was to assess the effects of ZA on the structural progression of spinal OA in postmenopausal women with pre-existing spinal radiographic OA, in a *post hoc* analysis of data from the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial (HORIZON PFT).[22]

Methods

The HORIZON PFT[22] was an international, multicenter, double-blinded, randomized control trial that evaluated the effectiveness of ZA (5 mg, IV) at baseline, 12, and 24 months, compared to placebo, in 7765 postmenopausal women with osteoporosis over a period of 36 months. Ethical approval, inclusion, and exclusion criteria for the horizon PFT have been published elsewhere.[22] In brief, the study was conducted in 27 countries and recruited postmenopausal women aged 65–89 with osteoporosis, defined as a femoral neck *T* score of $\leqslant -2.5$, or a *T* score of $\leqslant -1.5$ along with radiographic evidence of at least one moderate or two mild vertebral fractures. Non-bisphosphonate anti-resorptive therapy was allowed.

We performed a *post hoc* analysis, blinded to treatment allocation, of a subset of paired lateral spinal radiographs from the HORIZON PFT study. Paired radiographs of the thoracic levels T4–T12 and lumbar levels L1–L5 at baseline and 36 months were chosen using a computer-generated random sequence, until 500 includable sets were identified. The inclusion criteria were as follows: postmenopausal women who received at least one dose of study medication (ZA or placebo), and who had both baseline and 36 month spinal radiographs available, with a non-zero score for spinal OPh at baseline. Subjects were excluded if there were fractures seen on either the baseline or 36 month X-rays, or if the X-rays were unreadable secondary to poor image quality. Vertebral fractures were defined as a reduction in vertebral height of at least 20%.

Lateral spinal radiographs were scored paired in temporal sequence, by consensus of two readers (a rheumatology trainee (LH) and a consultant rheumatologist with 10 years of experience in scoring radiographs for structural changes (HK)), who were blinded to treatment. Radiographs were scored separately for OPh and disk space

narrowing (DN) using the current gold standard method for OA, based on an atlas of images at the time of reading.[22] Each level from T4–12 and L1–5 was assigned a score of 0–3. Data sets were included in the statistical analysis if at least five vertebral levels could be read. When using an ordinal scale, the smallest detectable difference is 1; however, the amount that can result in a clinically significant clinical change is not known.

Intraobserver (intrareader) variability was determined by rescoring the first 50 pairs of radiographs at a minimum of 1 week apart. Weighted kappa scores were calculated as 0.65 (considered substantial) for OPh and 0.55 (considered moderate) for DN.[23]

OPh and DN scores

The sum of OPh and DN scores from T4 to L5 (maximum score for OPh = 42, and for DN = 39) was computed for each subject. The difference between the sum at follow-up and the sum at baseline yielded a change in each summary score. We then calculated the mean difference in the change in the sum of OPh and DN scores from T4 to L5 from baseline to follow-up in each treatment arm, using linear regression.

Since there was very little DN in the thoracic spine, we additionally performed a subgroup analysis of the change in OPh and DN summary scores in the lumbar spine alone. An analysis stratified by baseline body mass index (BMI) (<25 kg/m^2 *vs* $\geqslant 25$ kg/m^2) was also undertaken to compare the change in OPh and DN between the low and high categories.

Using deltas from the Neogi paper[24] to calculate the sample size to achieve a power of 80%, 282 patients were required for the OPh score ($n = 141$ per group), and 670 patients ($n = 335$ per group) for the DN score.

Therefore, our study was sufficiently powered to detect a change in OPh scores between the groups; however, it was underpowered regarding small changes in DN. Nonetheless, the latter were unlikely to be clinically meaningful.

Results

All of the included patients were postmenopausal women, and Table 1 outlines their baseline characteristics.

A total of 504 sets of paired radiographs were included in the analysis, 245 in the ZA group (225 received all three infusions) and 259 (242 received all three infusions) in the placebo group.

We found that the distribution of the sum of osteophyte scores, which were approximately normally distributed, remained similar between baseline and 36-month radiographs.

The scores for DN were relatively low, mainly due to changes in the lumbar spine, with minimal disk narrowing occurring in the thoracic spine. The DN scores were approximately normally distributed. These scores did not differ over time.

The changes in the OPh and DN scores from baseline to 36 months were minimal. Table 2 demonstrates the change in OPh scores between the baseline and 36 months in the whole spine in both ZA and placebo groups (1.0 ± 1.6, 0.8 ± 1.3, respectively, $p = 0.1$).

Subgroup analysis of the lumbar spine changes also failed to show a statistical significance. Table 2 demonstrates non-significant changes in DN scores between the baseline and 36 months in the whole spine in both ZA and placebo groups (0.3 ± 1.0, 0.3 ± 0.8, respectively, $p = 0.4$).

No difference in changes in OPh or DN between the two treatment groups was observed in those with high or low BMI (<25 kg/m^2 *vs* $\geqslant 25$ kg/m^2). Table 3 shows the effect of treatment on changes in OPh and DN by BMI.

Discussion

In this *post hoc* analysis of a sample enriched for radiographic OA, the rates of changes in OPh and DN scores in postmenopausal women receiving ZA or placebo were small and did not differ between the ZA and placebo arms.

Here, we assessed a group of postmenopausal women with osteoporosis, traditionally considered to be a group likely to have a low incidence of spinal OA.[1,25] The studied sample (postmenopausal women with osteoporosis) could be considered as a source of selection bias that may limit the external validity of this study, as individuals with osteoporosis may have a lower incidence of OA. However, recent studies have failed to confirm a negative relationship between OA and osteoporosis.[26–28] In addition, as an elderly female

Table 1. Baseline characteristics of cohort.

Variable	Placebo (*N* = 259)	Zoledronic Acid (*N* = 245)	*p* value*
	Mean (SD) or no. of patients (%)		
Age (year)	72.7 (5.2)	72.4 (5.1)	0.51
Body mass index (kg/m^2)	25.2 (3.8)	25.7 (4.6)	0.17
Current smoking history	18 (7.0%)	16 (6.5%)	0.85
T score at the femoral neck			
<−2.5	146 (56.4%)	158 (64.5%)	0.07
−2.5 to −1.5	111 (42.9%)	85 (34.7%)	
> −1.5	1 (0.4%)	1 (0.4%)	
Previous medication use			
Estrogen replacement therapy	30 (11.6%)	31 (12.7%)	0.72
Bisphosphonates	32 (12.4%)	22 (9.0%)	0.22
Calcitonin	18 (7.0%)	18 (7.4%)	0.88
SERMs^	13 (5.0%)	12 (4.9%)	0.95
Mean spinal OA score baseline			
OPh*	19.2	20.0	0.31
DN≈	3.6	3.8	0.60

^SERM, selective estrogen receptor modulators; *OP, osteophytes whole spine; DN≈, disk space narrowing whole spine; **t*-test.

Table 2. Changes in mean OPh and DN scores in the whole and lumbar spine.

	ZA	Placebo	*p* value*
Osteophytes—mean score (SD)			
Baseline	20.0 (8.8)	19.2 (8.0)	
36 months	20.9 (9.0)	20.0 (8.1)	
Change whole spine	1.0 (1.6)	0.8 (1.3)	0.1
Change lumbar spine	0.3 (0.8)	0.3 (0.7)	0.4
Disk space—mean score (SD)			
Baseline	3.8 (4.6)	3.6 (4.2)	
36 months	4.1 (4.8)	3.9 (4.4)	
Change whole spine	0.3 (1.0)	0.3 (0.8)	0.7
Change lumbar spine	0.2 (0.7)	0.18 (0.6)	0.7

DN, disk space narrowing; OPh, osteophytes; ZA, zoledronic acid.
**t*-test.

cohort enriched to include individuals with hypertrophic OA at baseline, the cohort examined in this study was characterized by a high risk of progressive spinal OA.

The negative findings in this study differed from findings of some previous reports. A previous *post hoc* analysis of alendronate (5 mg/day for 2 years and then 10 mg/day in year 3) by Neogi *et al.*,[21] involving 200 patients, found a weakly significant change in mean total OPh and lumbar OPh (+3.2 (2.4–4.1) compared to +4.7 (3.7–5.7), $p = 0.04$, for total OPh). A non-significant halving of DN progression was identified ($p = 0.20$), with the majority of DN occurring in the lumbar spine. When lumbar spine DN was analyzed in isolation, there was a small but significant difference in the mean change in DN between the groups, favoring alendronate (+0.3 (0.2–0.5)) compared to +0.6 (0.4–0.8), $p = 0.04$). The authors proposed a role of bisphosphonates in altering the pathological processes seen in OA.[21]

Table 3. ANOVA coefficients of treatment predicting the change in OPh and DN by BMI.

	BMI	Coefficient	SE	*p* value	Lower bound CI	Upper bound CI
Difference in OPh	<25	−0.291	0.196	0.14	−0.67516	0.09316
	⩾25	−0.115	0.17	0.5	−0.4482	0.2182
Difference in DSN	<25	−0.098	0.11	0.38	−0.3136	0.1176
	⩾25	0.045	0.118	0.7	−0.18628	0.27628

OPh, osteophytes; DN, disk space narrowing; BMI, body mass index.

When comparing this study to the one by Neogi *et al.*,[21] both studies undertook *post hoc* analyses of trials involving postmenopausal women.[22,29] However, the subjects in our study were older (73 *vs* 66 years) and were selected for radiographic spinal OA at baseline. Methodologically, we utilized the same radiographic scoring system to assess OPh and DN, with acceptable intraobserver variability. Although, in contrast to the methodology used in the report of Neogi *et al.*, we excluded patients with vertebral fractures, which is an advantage of our approach. Our study may be considered underpowered based on data from the Neogi *et al.* study. However, ZA is likely to be a more potent structural modifier than aledronate; therefore, the much larger sample size in our study compared to the Neogi *et al.*'s study (500 *vs* 200) provides a more convincing evidence of a null effect of bisphosphonates on spinal OA progression.

A similar *post hoc* analysis was performed to compare the effects of 3-year strontium ranelate intake *versus* placebo in spinal radiographic OA. The findings of that study suggest that strontium ranelate could reduce the progression of lumbar spinal OA.[30] The population was pooled from two RCTs[31,32] but was similar to that presented in our study (postmenopausal women (mean age of 73 years) with osteoporosis, preselected for spinal radiographic OA). The positive findings of that study may derive from studying the lumbar spine only or may be related to the properties of the studied agent. Strontium ranelate is used for treatment of osteoporosis as it reduces bone resorption *via* an unknown mechanism.[31] However, potential cardiovascular side effects of strontium have led to the abandonment of further investigations of this drug in OA.[33]

Several randomized controlled trials have been undertaken to examine the structural modification and analgesic effects of bisphosphonates in OA and most of these studies examined the knee. Two meta-analyses found no clear effect of bisphosphonates on the structure, with conflicting results regarding the influence on symptoms.[7,34] The heterogeneity of published RCTs with regard to the bisphosphonate studied, the therapeutic potency, the duration of follow-up, and study outcomes are recognized as potential confounders.

Recently, Hayes *et al.* examined data from the osteoarthritis initiative (OAI) and found that bisphosphonates may inhibit radiographic progression of knee OA. The effect size was greater in non-overweight or obese subjects (BMI < 25 kg/m^2).[35] This is in contrast to our study, in which no statistical difference was seen between treatment effects in those with high and low BMI, although our study was not sufficiently powered for such an assessment. The Hayes *et al.* study was not a randomized controlled study (although it utilized propensity matching), but an observational study that examined the knee. Hayes *et al.*[35] also found that bisphosphonate had protective effects against structural disease progression in individuals with lower baseline radiographic scores. Abnormal subchondral bone turnover seen in early OA is similar to that seen in osteoporosis; therefore, earlier OA may be most amenable to bisphosphonate therapy.[36] By selecting individuals with a non-zero OPh score, we created a moderate OA cohort, with subjects potentially less likely to respond to ZA. In contrast, the cohort studied by Neogi *et al.* was younger and no osteophyte score floor was required at baseline, which may reflect an earlier OA cohort more susceptible to bisphosphonate treatment.[19]

Hayes *et al.* also hypothesized that individuals with poor subchondral bone quality are at a higher risk of microfractures and progressive OA. These patients may be more likely to benefit from

bisphosphonates if they are non-overweight and therefore less susceptible to damage from the weight-bearing load.[34] It is possible that as BMI increases, the potential benefits of bisphosphonates are becoming masked. Neogi *et al.* did not undertake a sub-analysis of individuals with a normal BMI (<25 kg/m^2).[21] In our analysis, ZA had no impact on the radiographic progression of OA of the spine in people with a BMI < 25 kg/m^2.

This study is not free from certain limitations. The lack of progression of OPh and DN in the placebo arm may indicate that radiographs are an insensitive way to visualize structural changes, and utilizing more sensitive imaging techniques, such as MRI, may be more useful in detecting such changes.

The small amount of overall change in both groups seen in this study suggests that demonstrating a significant difference in the studied parameters is difficult, even when mitigation of OA is achieved. In addition, our study is potentially not powered sufficiently to detect small changes; however, it is the largest analysis of the effects of bisphosphonates to date, focused on a potent agent. Moreover, our findings suggest that ZA does not affect DN or OPh progression. However, ZA may have a specific effect on Modic changes, which are seen in a subgroup of early OA, and are associated with low back pain.[37–40] Koivisto *et al.*[37] have demonstrated that in a subgroup of people with chronic low back pain and MC, ZA has an analgesic efficacy and leads to a significantly reduced non-steroidal anti-inflammatory drug (NSAID) burden. Our group has published similar results on pain but showed no change in the Modic size over 6 months,[19] which is consistent with the findings described in this manuscript.

There are potential confounding factors in our study cohort,[22] as inclusion criteria allowed for patients to be on concomitant hormone-replacement therapy, calcitonin, tibolone, tamoxifen, and medroxyprogesterone, or to have had previously been on bisphosphonates. For bisphosphonates, a washout period was required before ZA administration, and the length of this period was dependent on the duration of bisphosphonate use. Overall, 14.4% of patients in the placebo group and 14.6% of patients in the ZA group had been on bisphosphonates prior to the study. In addition, many of the patients in the study used NSAIDs before and during the study period. Glucocorticoids were much less commonly used, usually for relatively short periods of time. It is unclear whether this had any influence on the observed results, but it is unlikely that any of these factors are causally related to OA and that they were imbalanced between the groups.

Given the large cohort of longitudinal information available to study, particularly radiographs, fracture trials lead to analyses like the one we conducted here. However, these trials are invariably performed in selected patient populations at risk of fracture (usually postmenopausal women); therefore, caution needs to be taken when translating the findings of such trials to the general population and particularly to men.

Conclusion

In this patient subgroup enriched for radiographic OA, ZA treatment over 3 years was not associated with slowing of progression of OPh or DN in the thoracolumbar spine.

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Author contributions

L.V. Host: Data curation; Project administration; Writing – review & editing.

H.I. Keen: Data curation; Funding acquisition; Methodology; Writing – original draft; Writing – review & editing.

L.L. Laslett: Methodology; Writing – original draft; Writing – review & editing.

D.M. Black: Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

G. Jones: Conceptualization; Funding acquisition; Methodology; Supervision; Writing – review & editing.

Conflict of interest statement

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Ethical approval information

This was a *post hoc* analysis of data from a previously published RCT, and as such, it did not require a specific HREC approval (ClinicalTrials.gov number: NCT00049829).

ORCID iD

H.I. Keen https://orcid.org/0000-0002-8469-2424

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