Research Article

Journal of Bone Biology and Osteoporosis

Continuing Relief of Pain with Long Term Treatment for Osteoporosis with Intravenous Pamidronate

Wilson S^{1,3}, Sharp CA^{2,3} and Davie MWJ^{3*}

¹School of Sport Health and Exercise Sciences, Bangor University, UK

²Chester Medical School, University of Chester (University Centre Shrewsbury), Guildhall, Shrewsbury, UK

³Charles Salt Centre for Human Metabolism, Robert Jones and Agnes Hunt Hospital, Oswestry, Shropshire, UK

***Correspondence:** Michael W. J. Davie, Charles Salt Department for Human Metabolism, Robert Jones and Agnes Hunt Hospital, Oswestry, SY10 7AG, UK, Tel: (+)1691 404603; Fax: (+)1691 404056; E-mail: mike.davie@nhs.net

Rec date: June 29, 2018; Acc date: Aug 06, 2018; Pub date: Aug 10, 2018

Abstract

Purpose: Bisphosphonates are valuable in reducing the incidence of fracture. Side effects limit persistence with oral therapy and long term studies of pain relief are difficult to pursue. Intravenous bisphosphonates offer an alternative treatment to oral bisphosphonates and are tolerated over a longer period. The use of Pamidronate, an intravenously administered bisphosphonate, to benefit pain and reduce fracture incidence in the long term has not been extensively investigated. The study aimed to investigate the effect of Pamidronate on pain, vertebral fracture incidence and Bone Mineral Density over 6 or more years.

Methods: Patients were offered intravenous Pamidronate if oral treatment with bisphosphonates or Hormone replacement therapy had failed due to side effects, fractures continued on oral treatment or oesophageal reflux led to cessation of oral treatment. Pain was assessed using the Nottingham health profile; radiographs were used to evaluate vertebral fracture and DXA measured bone mineral density.

Results: The primary outcome was the pain domain. Median patient follow up was 9 years. Pain had improved significantly ($p = 0.03$) and in 68% pain had either improved or remained unchanged. Vertebral fractures occurred in 14% of patients in the first 3 years, 9.5% in years 4-6, but increased in years 7-9 to 27%. Bone mineral density increased in the lumbar spine ($p < 0.001$) but not at the femoral neck.

Conclusions: Pamidronate had a beneficial effect on pain over the period of the study. Vertebral fracture incidence increased after 6 years of Pamidronate, although spine BMD increased significantly.

Keywords: Pamidronate, Pain relief, Long term, Vertebral fracture

Introduction

Vertebral fracture is frequently associated with pain. This may improve over 6-8 weeks, but many patients continue to complain of chronic back pain. Oral bisphosphonate treatment is effective at reducing the incidence of vertebral fracture, but its use is limited by the incidence of side effects, particularly of a gastro-intestinal origin. Thus, initiation of therapy and compliance remain significant problems with oral bisphosphonate [1]. Before the advent of zoledronic

acid, the only alternative for many patients requiring intravenous bisphosphonate treatment to avoid upper gastrointestinal irritation was intravenous Pamidronate.

The response of pain to bisphosphonate treatment has been reported for low Bone Mineral Density (BMD) with oral alendronate treatment over 1 year using the Nottingham Health profile [2], for patients with acute vertebral fracture following intravenous Pamidronate [3-5], and for chronic back pain due to causes other than

vertebral collapse or radiculopathy [6]. These studies have been of short duration with the Pamidronate studies lasting only a maximum of 6 months and the oral study for 1 year.

Data relating to the effects of longer term treatment with bisphosphonates with regard to pain in osteoporosis are parsimonious. The present study with intra venous Pamidronate was designed to follow patients with very low BMD with or without fractures and who complained of back pain. They were deemed to have failed on the treatment available at the time or had gastro-oesophageal symptoms precluding use of an oral bisphosphonate. The primary aim was to investigate whether pain had improved between the commencement of Pamidronate and the time when Pamidronate treatment was discontinued – usually in favour of more recent treatments such as zoledronic acid or parathyroid hormone. Secondary aims were to investigate whether BMD improved, whether fracture incidence decreased and what the effect of Pamidronate was on other domains of quality of life.

Patients and Methods

Patients (all Caucasian) were offered intravenous Pamidronate (Ciba Geigy/Novartis, Basel, Switzerland) if they reported side effects or if they exhibited worsening BMD or vertebral fracture. Five patients had Crohns disease or colitis and one was found to have coeliac disease. Hypothyroidism was a feature in five patients. Three had epilepsy (controlled) and 3 had a history (in the past) of breast or lung cancer. There was no evidence to suggest skeletal involvement in patients with a past history of cancer. Three patients (one with Behcet's disease, one having had a renal transplant and one with Crohn's disease) had been exposed to corticosteroids in the past. Other conditions included one case each of Psoriasis, Deep Venous thrombosis, Hereditary Spherocytosis and Primary Biliary Cirrhosis. Twelve patients were known to have significant gastric or oesophageal disease or had had surgery to the upper Gastro-intestinal tract. Previous treatments for osteoporosis had been for less than one year in 12 patients, 1-3 years in 6 patients and more than 3 years in 6 patients. In 11 patients the previous duration of treatment was not recorded.

Treatment cut off was in 2008 by which time other treatments had been licensed. Patients could take analgesics if required. Pamidronate was given by i/v infusion in 0.5l 0.9% saline over 3 hours. Pamidronate was given either twice or 4 times a year, the average annual dosage being 350 ± 106 mg/yr.

Radiographs were taken initially with intermediate radiographs at an average of 3yr intervals and before the cessation of Pamidronate treatment. Vertebrae from D2 to L4 were examined. An initial criterion of 20% or more anterior or crush deformity was required for a fracture with subsequent fractures requiring a decrement of 20% or greater. Radiographs were all taken using standard radiographic procedures.

Bone mineral density (BMD) was determined initially on some patients using a Hologic QDR 1000 densitometer and all patients finally on Hologic 4500A equipment (Hologic, Marlborough, Mass, USA). BMD was measured at L2-4 inclusive and at the femoral neck according to manufacturer specifications for normal clinical use. Since the two machines give slightly different BMD values, a series of 118 healthy normal subjects was examined on both machines on the same day. The % difference of BMD between the two machines was calculated as $(\% \text{ diff } \{(1000 \text{ value} - 4500 \text{ value}) / 1000 \text{ value}\} \times 100)$. The difference was -0.08% for the lumbar spine and -1.64% for the femoral neck (viz. QDR4500 gave a slightly higher reading than the QDR1000). Each final value, if appropriate, was adjusted by this percentage. The smallest detectable difference was 5.3% at the spine and 6.5% at the femoral neck. These values are comparable with previously reported differences [7,8] and other authors have applied similar adjustment to data from studies embracing two different densitometers [9] although other reports have expressed misgivings about comparing results from pencil beam and Fan beam technologies [10]. T scores (number of standard deviations patient's BMD differed from peak bone mass) were calculated from the peak bone mass in women for the spine (1.102 ± 0.132 g/cm²) and femoral neck (0.871 ± 0.108 g/cm²) [11] and in men for the spine (1.08 ± 0.11 g/cm²) and femoral neck (0.96 ± 0.13 g/cm²) [12].

Quality of life measurements were made using the Nottingham Health Profile (NHP) [13], a quality of life tool that includes pain as a separate domain. The NHP was a widely used Quality of life instrument at the time when the first patients began receiving treatment. All patients with osteoporosis routinely had quality of life assessment. High scores indicate greater suffering than low scores. Patients were generally in Social Class III and non-manual (Class IIInm). The raw data are reported. However the age related means [13] were used to identify patients below (i.e. better than) average. No attempt was made to identify whether ceiling scores might have improved (i.e. whether pain had improved from terrible to mildly terrible whilst

still scoring the highest score) and similarly for floor scores. All patients were asked to complete this both initially and at the end of their treatment for clinical purposes.

Simple statistical testing was used as appropriate. The Shapiro-Wilk test was applied to investigate for normality. Differences between groups were tested using Student's *t*-tests for independent or dependent variables, or for non-parametric data Mann Whitney U test, and Wilcoxon test. Differences in proportions were tested by Chi squared or Binomial testing. Correlation was investigated using Pearson correlation coefficient or Spearman rank tests. Probability of less than 0.05 was assumed to be significant. Data that was not significant are reported as ns. Interquartile ranges (IQR) were calculated for non-parametric data. Data are presented as mean $\pm$ Standard Deviation (SD) or as Median (Interquartile Range (IQR)).

Results

Baseline data

Baseline data appear in table 1. Women ($n = 31$, age 62.7 ± 8.8 yr) were older than men ($n = 12$ 52.9 ± 9.9 yr) ($p < 0.01$). The NHP was completed by 33 patients. The pain domain scored the highest of all the domains. There was no significant relationship between Pain scores and spine or femoral neck BMD or fracture number. The patients did however show significant morbidity with only a minority having NHP scores in the range of good health. Ten men and 25 women had osteoporosis (T scores more than 2.5 Standard deviations below peak bone mass) at the spine or femoral neck. Six men and 20 women of the group who completed a NHP had osteoporosis at spine or femoral neck. Most patients had been on treatment for osteoporosis prior to starting Pamidronate. More than half of the patients starting treatment had either progressive osteoporosis on existing treatment or had indigestion.

Spine fractures were present in 11 men and 23 women. The most frequent sites in men were D6 and 7 and in women D7 and 8. There were no significant correlations between fracture number and BMD at either spine or femoral neck. Nine patients (1 man, 8 women) had no vertebral fractures at baseline. In this group T score at the spine was -2.67 ± 0.67 (mean $\pm$ SD) and at the femoral neck -3.05 ± 1.34 . Those with a baseline vertebral fracture had a spine T score of -2.86 ± 1.04 and a femoral neck T score of -2.78 ± 1.76 . A vertebra between L2 and L4 was affected by a significant deformity in 7 patients.

Women had sustained 8 wrist fractures, 2 upper femur

fractures and 3 fractures affecting each of the upper and lower limbs. Men had suffered 1 wrist fracture, 1 upper femur fracture and 3 lower limb fractures.

Final data

Results following treatment appear in tables 2 and 3. All patients completed 5 years of Pamidronate; 42 completed 6 years and 27 were still receiving Pamidronate after 9 years, the average number receiving Pamidronate in years 7-9 being 33. No patient died in the course of the study and all were transferred to alternative treatments. All patients received their Pamidronate dosage appropriately. Median treatment time was 9 yr (IQR = 4). Thirty two patients completed a NHP at the end of the study. Of these 6 men and 20 women initially had osteoporosis at the spine or femoral neck.

Thirty one patients completed a NHP pain profile before and at the end of treatment. Pain improved in 16 patients, showed no change in 5 and deteriorated in 10. An alternative post hoc null hypothesis was that over the average duration of this study pain was likely to deteriorate. Twenty one patients improved or were the same compared with 10 who deteriorated (Table 3). A binomial test (one sided: pain improved or did not deteriorate vs. deterioration) showed a significant result ($p < 0.036$). Ten patients in the study had no causes for pain other than osteoporosis and had also completed an NHP profile before and at the end of the study. Of these the median NHP pain score before treatment was 48 (IQR37) and at the end of the study 38 (41). Three patients had dropped into the NHP pain range for healthy subjects, 8 had improved, one stayed the same and one deteriorated. A two tailed binomial test on this small sample showed a probability of 0.057 (5.7%) that the improvement would have happened by chance. Patients who were treatment naïve at the start of treatment showed no greater improvement in pain scores than those previously treated. Changes in other domains of the Nottingham Health profile appear in table 3. For all patients, the physical mobility domain was the only one in which the numbers worse at the end of treatment exceeded those either better or the same.

Eleven of the 13 patients sustaining a fracture during the study completed a NHP: in these patients pain scores declined (i.e., improved) by 18% by the end of the study. Change in pain score did not relate to duration of treatment, age at the start, initial pain score, BMD scores (initial, final or change), initial fracture prevalence or number of new fractures.

BMD in the spine increased from $0.74 \pm 0.12 \text{ g/cm}^2$ to $0.84 \pm 0.13 \text{ g/cm}^2$ ($p < 0.001$) whereas the difference between starting FN BMD ($0.56 \pm 0.12 \text{ g/cm}^2$) and final BMD ($0.57 \pm 0.11 \text{ g/cm}^2$) was not significant. Change of BMD (expressed as percentage change) at the spine ($15.5 \pm 18.2\%$) was greater than the change at the femoral neck ($7.7 \pm 36.1\%$) ($p < 0.01$).

After 3 years, 5 patients (12%) had sustained 7 vertebral fractures. Between years 3.1-6 yr a further 4 patients (10%) had 5 vertebral fractures. In the third 3 year period (years 7-9), 13 fractures were recorded in 7 patients out of a mean of 33 patients (21%) remaining on Pamidronate in those years (Chi squared = ns). Bone mineral density was not significantly lower in those who sustained fractures compared with those who did not.

Discussion

Significant improvement in back pain has been shown to follow the use of Pamidronate in acute vertebral collapse [3-5]. The present study, though without the benefit of a control group, which would have been ethically impossible, suggests that the majority of patients with severe osteoporosis receiving Pamidronate therapy in our study experienced no deterioration in pain and in many instances improved. Abolition of pain is not achieved in all patients treated with bisphosphonate. In the Horizon study of zoledronic acid in women with osteoporosis over 3 years the proportion of patients reporting back pain fell from 73% to 56.6% (fall of 16.4%) in the zoledronic acid treated group compared with 72% to 59.5% in the control group [14]. In our study the proportion of all patients reporting pain above the age related mean fell from 97% to 87.5% (Table 2) – a decline of 9.5% and in women the proportion reporting pain fell by 12% from 96% to 84%. That time itself may lead to improvement of back pain was suggested by the Horizon trial of zoledronic acid in female patients.

Whereas abolition of pain may be ideal, improvement in pain is also desirable. All the studies including the present one show that bisphosphonates can have a statistically significant beneficial effect on pain in the presence of osteoporosis. The percentage improvements in pain in osteoporosis are difficult to compare because of different methodology and entry criteria, but all show that improvement was limited. The greatest improvement in pain was in patients with vertebral compression fracture whose pain improved by 50% after 30 days (4). Another study of zoledronic acid using Qualeffo over 12 months in women with a T score -2.5 or lower also showed an

improvement of 20% in pain scores [15]. The least improvement was 7% using Zoledronic acid in women with T scores at the femur or spine below T-2.5 after 24 months [16]. The present study covers a median treatment time of 9 yr in the course of which there was a 26% improvement in pain in female patients (Tables 1 and 2). Data from our study and others suggest that there is a great benefit to be had initially, but that in the longer term pain relief is less but still significant (Figure 1).

Figure 1: Decline in % improvement in pain with time after starting bisphosphonate. Numbers adjacent to data points refer to reference number. Data are taken from Ref 4 (0.08 yr), 2 (1 yr), 15, 16 (2 yr) and present (9 year) and are calculated as $\{(initial-final)/initial\} \times 100$. Note that entry criteria and methodology vary between studies. Apart from ref 4 which had 65% females, all other studies relate to females only. The trendline depicts the relationship between improvement and logarithm of time.

However, around half of patients (Table 2) were showing an improvement in pain, whilst in two thirds pain had improved or had not changed. Even in patients who sustained fractures, there was an improvement in pain. The reason for this improvement, which is similar to that found in acute studies, is uncertain. The pain of a new acute fracture during treatment may be masked by Pamidronate, as in the acute studies. Patients may acclimatise to pain or undertake less activity. Evidence for the last is supported by the deterioration in the NHP mobility domain (Table 3) at the end of the study (although statistically the deterioration was not significant). The observation that the emotional domain improved as much as the pain domain may indicate that patients were coming to terms with their condition, although values were not high initially (Table 1).

Inhibitors of bone resorption such as calcitonin or bisphosphonates have been associated with improvement in pain, usually in acute situations, in a number of disease states affecting bone such as Paget's disease, reflex sympathetic dystrophy (chronic regional pain syndrome) and SAPHO [17,18]. There was no evidence that an increase in BMD over time was associated with improvement in pain. Many of the studies of bisphosphonates in the acute osteoporotic situation using Quality of life tools mention an improvement of pain, but no improvement in physical mobility or energy. Patients, in whom vertebral collapse had been excluded, treated with Pamidronate for low back pain show an improvement in pain scores [6]. Similar

reports of acute improvement in back pain have been recorded in patients treated with zoledronic acid, but the effect was not maintained at one year [19]. Patients in the present study may have suffered back pain initially from the osteoporotic collapse, but pain thereafter may have derived from other structures. Collapse of a vertebra may alter spinal anatomy sufficiently to cause arthritis in the posterior facet joints. Data for use of bisphosphonates in osteoarthritis are conflicting [20]. Pain scores on a numeric rating scale may improve but more formal assessments of osteoarthritis fail to show significant change [21]. Additionally, improvement may also be dependent on the time after dosing [22]. In an experimental arthritis

Table 1: Baseline data.

	Male	Female	All
	12	31	43
Age at baseline yr (mean±SD)	52.9±9.9	62.7±8.8 §	59±10.0
Lumbar spine BMD g/cm2 (mean±SD)	0.741±0.144	0.738±0.108	0.739±0.117
Femoral Neck BMD g/cm2 (mean±SD)	0.523±0.125	0.573±0.123	0.559±0.124
Spine T score (mean±SD)	-3.07±1.31	-2.76±0.82	-2.85±0.97
Femoral Neck T score (mean±SD)	-2.83±1.12	-2.76±1.14	-2.78±1.12
Number vertebral fractures (Median (IQR)) #	2(4)	3(4)	3(4)
Number of patients without vertebral fracture	1	8	9
Number of patients receiving previous treatment	8¶	27Ø	35
Reasons for Starting Pamidronate †			
Back Pain	4	8	12
Progressive Osteoporosis on treatment	5	10	15
Fractures on Treatment	0	2	2
Indigestion	3	12	15
Number completing NHP	7	26	33
NHP domain (median (IQR))			
Energy	37(76)	61(76)	61(76)
Pain	40(52)	67(41)	61(43)
Emotion	10(51)	10(32)	10(33)
Sleep	38(70)	45(50)	40(55)
Social	20(80)	0(23)	0(23)
Physical mobility	34(13)	44(24)	44(22)
Number of patients with NHP values below age related mean (i.e. in good health)			
Energy	1	4	5
Pain	0	1	1
Emotion	1	13	14
Sleep	3	5	8
Social	2	17	19
Physical mobility	0	1	1

§ Significantly older than men p < 0.01

IQR: Interquartile range

¶ 7 on bisphosphonate, 1 on decadurabolin

Ø 20 on bisphosphonate, 5 on oestrogen replacement therapy, 1 on fluoride, 1 on decadurabolin

† Some patients had more than one reason.

model in the rabbit zoledronic acid protected against the degradation of collagen [23], whilst in mice Pamidronate reduced the degradation of cartilage in mice exposed to experimental meniscectomy [24]. If the anatomy of the spine is deranged after vertebral fracture, osteoarthritis may supervene and bisphosphonates may help protect against collagen destruction. The present study suggests that any improvement in pain in this group of patients was unrelated to BMD or fracture incidence.

Whilst Pamidronate had a positive effect on pain and on BMD in the spine, the effect on fracture incidence was less evident. The patients in the present study were at relatively high risk having a significant past history of fracture and comparison with other studies is difficult. Nevertheless, compared with alendronate in patients at the highest risk of fracture over 3 years [25], patients receiving Pamidronate had a similar incidence in the first

Table 2: Final Data.

	Male	Female	All
Number	12	31	43
Duration of treatment yr (Median (IQR))	11(2.5)	9(3)	9(4)
Lumbar spine BMD g/cm ² (mean±SD)	0.846±0.112†	0.835±0.139	0.835±0.131
Femoral Neck BMD g/cm ² (mean±SD)	0.559±0.120†	0.575±0.109 Ø	0.570±0.108
Lumbar spine T score (mean±SD)	-1.95±0.93	-2.08±1.11	-2.00±0.95
Femoral neck T score (mean±SD)	-3.08±0.93	-2.75±0.96	-2.84±0.95
No patients with new vertebral fracture #	2	14	16
Number completing NHP	7	24	31
Domain of NHP			
Energy (Median (IQR))	24(39)	61(76)	61(64)
Pain (Median (IQR))	47(44)	49(69)	49(64)
Emotion (Median (IQR))	7(18)	7(34)	7(27)
Sleep (Median (IQR))	34(80)	35(45)	35(54)
Social (Median (IQR))	0(19)	0(23)	0(22)
Physical mobility (Median (IQR))	42(23)	55(36)	55(36)
No of patients with values below age related mean			
Energy	1	4	5
Pain	0	4	4
Emotion	3	13	16
Sleep	3	7	10
Social	5	17	22
Physical Mobility	0	3	3

† BMD at spine and femur not available for 1 man

Ø 2 women did not have final femur scans of satisfactory quality

IQR: Interquartile range

Up to 9 years

Table 3: NHP Profile changes.

Comparison with Baseline	Male			Female			All		
	Better	Same	Worse	Better	Same	Worse	Better	Same	Worse
Energy	4	2	1	5	9	10	9	11	11
Pain	2	2	3	14	3	7	16	5	10
Emotion	6	0	1	9	6	9	15	6	10
Sleep	2	1	4	9	7	8	11	8	12
Social	5	1	1	5	15	4	10	16	5
Physical Mobility	1	3	3	6	4	14	7	7	17
Total	20	9	13	48	47	50	68	53	65

3 years. The incidence increased with time and during the third 3 year period 21% sustained a fracture, although the different proportions failed to reach significance. Such a trend towards increasing fractures in the later years suggesting that the effect of Pamidronate waned as time passed. A similar, though less marked, progression of morphometric vertebral fracture was noted in the Horizon trial [26,27]. The significant effect of Pamidronate on spine BMD compared with little effect on femoral neck BMD may reflect a difference of Pamidronate action on cortical versus cancellous bone.

This study does have limitations. The number of patients was small, there was no control group and it was an observational study. The group was heterogeneous and few patients had osteoporosis in the absence of other pathology. However, in this small group for whom there were NHP data before and after the study, 8 out of 10 were showing improvement in pain scores. Strengths include the duration of the study and the effects on BMD and vertebral fracture over a long period in a group of patients with severe osteoporosis.

The present data indicate that Pamidronate has a significant effect on improving the pain component of a quality of life instrument over a long period of time and thus may have a useful role in the management of pain in patients with osteoporosis. The mechanism by which this is achieved remains uncertain, and the effect of Pamidronate on acute pain following vertebral collapse may differ from that experienced long term. The effect on vertebral fracture in severe cases of osteoporosis appears similar to alendronate in the first 3 years.

Conflicts of Interest

Sally Wilson, Christopher Sharp and Michael Davie have no interests to declare.

References

1. Dugard MN, Jones TJ, Davie MWJ. Uptake of treatment for osteoporosis and compliance after bone density measurement in the community. *Journal of Epidemiology & Community Health*. 2010;64(6):518-522. doi: <http://dx.doi.org/10.1136/jech.2008.084558>
2. Dursun N, Dursun E, Yalçın S. Comparison of alendronate, calcitonin and calcium treatments in postmenopausal osteoporosis. *Int J Clin Pract*. 2001;55(8):505-509.
3. Abdulla AJ. Use of pamidronate for acute pain relief following osteoporotic vertebral fractures. *Rheumatology*. 2000;39(5):567-568. doi: <http://dx.doi.org/10.1093/rheumatology/39.5.567>
4. Armingeat T, Brondino R, Pham T, Legré V, Lafforgue P. Intravenous pamidronate for pain relief in recent osteoporotic vertebral compression fracture: a randomized double-blind controlled study. *Osteoporosis International*. 2006;17(11):1659-1665. doi: <http://dx.doi.org/10.1007/s00198-006-0169-z>
5. Laroche M, Cantogrel S, Jamard B, et al. Comparison of the analgesic efficacy of pamidronate and synthetic human calcitonin in osteoporotic vertebral fractures: a double-blind controlled study. *Clinical Rheumatology*. 2006;25(5):683-686. doi: <http://dx.doi.org/10.1007/s10067-005-0159-0>
6. Pappagallo M, Breuer B, Lin H-M, et al. A pilot trial of intravenous pamidronate for chronic low back pain: *Pain*. 2014;155(1):108-117. doi: <http://dx.doi.org/10.1016/j.pain.2013.09.016>
7. Kolta S, Ravaud P, Fechtenbaum J, Dougados M, Roux C. Follow-up of Individual Patients on Two DXA Scanners of the Same Manufacturer. *Osteoporosis International*. 2000;11(8):709-713. doi: <http://dx.doi.org/10.1007/s001980070070>
8. Barthe N, Braillon P, Ducassou D, Basse-Cathalinat B. Comparison of two Hologic DXA systems (QDR 1000 and QDR 4500/A). *The British Journal of Radiology*. 1997;70(835):728-739. doi: <http://dx.doi.org/10.1259/bjr.70.835.9245885>
9. Looker AC, Melton LJ, Borrud LG, Shepherd JA. Changes in femur neck bone density in US adults between 1988-1994 and 2005-2008: demographic patterns and possible determinants. *Osteoporosis International*. 2012;23(2):771-780. doi: <http://dx.doi.org/10.1007/s00198-011-1623-0>
10. Henzell S, Dhaliwal SS, Price RI, et al. Comparison of Pencil-Beam and Fan-Beam DXA Systems. *Journal of Clinical Densitometry*. 2003;6(3):205-210. doi: <http://dx.doi.org/10.1385/JCD:6:3:205>
11. Davie M. Fractures at specific sites indicate low bone mineral density at lumbar spine and femoral neck in women. *Journal of Orthopaedic Rheumatology*. 1996;9:41-45.
12. Evans SF. Vertebral fractures and bone mineral density in idiopathic, secondary and corticosteroid associated osteoporosis in men. *Annals of the Rheumatic Diseases*. 2000;59(4):269-275. doi: <http://dx.doi.org/10.1136/ard.59.4.269>
13. Alonso JM, Bucquet D, Hunt S, Niero M, Wiklund I. European Guide to the Nottingham Health Profile.

Montpellier, France: European Group for Quality of Life and Health Measurement. 1989.

14. Cauley JA, Black D, Boonen S, et al. Once-yearly zoledronic acid and days of disability, bed rest, and back pain: Randomized, controlled HORIZON Pivotal Fracture Trial. *Journal of Bone and Mineral Research*. 2011;26(5):984-992. doi: <http://dx.doi.org/10.1002/jbmr.292>
15. Gokosmanoglu F, Varim C, Atmaca A, Atmaca M, Colak R. The effects of zoledronic acid treatment on depression and quality of life in women with postmenopausal osteoporosis: A clinical trial study. *Journal of Research in Medical Sciences*. 2016;21(1):112. doi: <http://dx.doi.org/10.4103/1735-1995.193503>
16. Huang S, Lin H, Zhu X, Chen X, Fan L, Liu C. Kwas zoledronowy stosowany przez dwa lata u Chinek z osteoporozą pomenopauzalną zwiększa gęstość mineralną tkanki kostnej i poprawia jakość życia związaną ze stanem zdrowia. *Endokrynologia Polska*. 2014;65(2):96-104. doi: <http://dx.doi.org/10.5603/EP.2014.0014>
17. Slobodin G, Rosner I, Feld J, et al. Pamidronate treatment in rheumatology practice: a comprehensive review. *Clinical Rheumatology*. 2009;28(12):1359-1364. doi: <http://dx.doi.org/10.1007/s10067-009-1256-2>
18. Guignard S, Job-Deslandre C, Sayag-Boukris V, Kahan A. Pamidronate treatment in SAPHO syndrome. *Joint Bone Spine*. 2002;69(4):392-396. doi: [http://dx.doi.org/10.1016/S1297-319X\(02\)00419-0](http://dx.doi.org/10.1016/S1297-319X(02)00419-0)
19. Koivisto K, Kyllönen E, Haapea M, et al. Efficacy of zoledronic acid for chronic low back pain associated with Modic changes in magnetic resonance imaging. *BMC Musculoskeletal Disorders*. 2014;15(1). doi: <http://dx.doi.org/10.1186/1471-2474-15-64>
20. Davis AJ, Smith TO, Hing CB, Sofat N. Are Bisphosphonates Effective in the Treatment of Osteoarthritis Pain? A Meta-Analysis and Systematic Review. Eldabe S, ed. *PLoS ONE*. 2013;8(9):e72714. doi: <http://dx.doi.org/10.1371/journal.pone.0072714>
21. Laslett LL, Kingsbury SR, Hensor EMA, Bowes MA, Conaghan PG. Effect of bisphosphonate use in patients with symptomatic and radiographic knee osteoarthritis: data from the Osteoarthritis Initiative. *Annals of the Rheumatic Diseases*. 2014;73(5):824-830. doi: <http://dx.doi.org/10.1136/annrheumdis-2012-202989>
22. Laslett LL, Doré DA, Quinn SJ, et al. Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial. *Annals of the Rheumatic Diseases*. 2012;71(8):1322-1328. doi: <http://dx.doi.org/10.1136/annrheumdis-2011-200970>
23. Lampropoulou-Adamidou K, Dontas I, Stathopoulos IP, et al. Chondroprotective effect of high-dose zoledronic acid: An experimental study in a rabbit model of osteoarthritis: AN EXPERIMENTAL STUDY. *Journal of Orthopaedic Research*. 2014;32(12):1646-1651. doi: <http://dx.doi.org/10.1002/jor.22712>
24. Funck-Brentano T, Lin H, Hay E, et al. Targeting Bone Alleviates Osteoarthritis in Osteopenic Mice and Modulates Cartilage Catabolism. Vanacker J-M, ed. *PLoS ONE*. 2012;7(3):e33543. doi: <http://dx.doi.org/10.1371/journal.pone.0033543>
25. Ensrud KE. Treatment with alendronate prevents fractures in women at highest risk: results from the Fracture Intervention Trial. *Archives of Internal Medicine*. 1997;157(22):2617-2624. doi: <http://dx.doi.org/10.1001/archinte.157.22.2617>
26. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of Zoledronic acid treatment of osteoporosis: A randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *Journal of Bone and Mineral Research*. 2012;27(2):243-254. doi: <http://dx.doi.org/10.1002/jbmr.1494>
27. Black DM, Reid IR, Cauley JA, et al. The Effect of 6 versus 9 Years of Zoledronic Acid Treatment in Osteoporosis: A Randomized Second Extension to the HORIZON-Pivotal Fracture Trial (PFT): EFFECT OF 6 VERSUS 9 YEARS OF ZOLEDRONIC ACID TREATMENT. *Journal of Bone and Mineral Research*. 2015;30(5):934-944. doi: <http://dx.doi.org/10.1002/jbmr.2442>

Copyright: © **Wilson et al.** This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.