CLINICAL STUDY

The effect of alendronate in the treatment of postmenopausal osteoporosis

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Abstract

Objectives: **The aim of the study was the evaluation of the effect of alendronate in the treatment of postmenopausal osteoporosis on subjective criteria and on bone mineral density after two years.**
Material and methods: **The authors collected data from 44 women by questionaire and analysed the data from DEXA examination. The patients were given Fosamax 10 mg and calcium 500 mg per day in the years 2001–2002.**
Results: **The compliance of alendronate was good in 42 women (95.5 %). 15 patients were very satisfied with the treatment, 22 were satisfied and 5 patients claimed no improvement at the end of the study. A positive effect of the treatment was seen in 37 patients (88.1 %). 21 patients claimed to have no pain and 15 patients suffered mild intermitent pain at the end of the study. 24 patients used no analgetics and 9 patients used them irregularly. 11 patients claimed to have normal activity and 22 patients had mildly diminished activity in daily life. The authors encountered no symptomatic vertebral or nonvertebral fracture during the study.**
The mean BMD in the lumbar spine improved in T score by 0.38 SD after one year and 0.35 SD after the second year. The mean BMD has improved in the neck region in T score by 0.21 SD after the first year and 0.21 SD after the second year.
The mean BMD in lumbar spine has improved in Z score by 0.31 SD after one year and 0.02 SD after the second year. The mean BMD in the neck region has improved in Z score by 0.31 SD after the first year and 0.16 SD after the second year.
The mean change of bone mineral density in lumbar spine was +4.17 % after the first years and +4.19 % after the second year. The mean change of BMD in the femoral neck region was +4.46 % after the first years and + 3.71 % after the second year.
According to student t-test all the data of increased BMD were statisticaly significant at the 5 % level of the significance ($p<0.05$).
Conclusion: **Alendronate therapy significantly reduced the pain and the need for analgesics. It improved the daily activity and mobility of the spine in the patients with postmenopausal osteoporosis. It resulted in a positive change of BMD in vertebral region of +8.36 % and +8.17 % in the femoral neck region after two years. The fracture risk in vertebral region was diminished by 31 % and in the femoral neck region by 38 % at the end of the study.** ***(Tab. 11, Ref. 14.)***
Key words: alendronate, postmenopausal osteoporosis, bisphosphonates, vertebral fractures, peripheral fractures.

Osteoporosis is a challenging problem in the countries with the increasing average life span. It is the cause of chronic backache and of vertebral and peripheral fractures. It diminishes the quality of life and increases morbidity. 9/10 of all fractures are caused by osteoporosis. The most serious is the fracture of the proximal femur. Mortality of patients with fracture of the neck of the femur is 20 % during the first year after the accident. Post-

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menopausal osteoporosis is the most common type. It involves 80 % of all types of the disease. Its incidence in women is 1 % before menopause, 25 % at 60 years and 50 % at 80 years of life. One of 5 women with a vertebral fracture sustains another vertebral fracture by the end of the first year. Two thirds of women with a fracture of the neck of the femur do not get the same level of activity after fracture healing.

Postmenopausal osteoporosis can be treated by several means-increased calcium dietary uptake with vitamin D (5), by hormone replacement therapy, by raloxifen as an selective modulator of estrogen receptors, by calcitonin (1) and by bisphosphonates (8). One of the most efficient bisphosphonates is alendronate (Fosamax, Merck-Sharp Dome Inc.).

The aim of the study was to assess the effect of Fosamax in a group of postmenopausal women on symptoms caused by osteoporosis and on bone mineral density values.

Material and methods

There were 90 patients treated with alendronate in the years 2001–2002 at the Ist Orthopaedic Department of St. Anna's Hospital of Masarykiensis University, Brno, Czech republic, in the years 2001–2002. There were 44 women with postmenopausal osteoporosis, which fullfilled the following criteria:

– bone mineral densitometry (DEXA) examination: T score less than -2.5 SD and Z score less than 1.0 SD. 1 SD (standard deviation = 10 % of bone mineral density),

– biochemical analysis (pyridonolin, deoxypyridinolin, osteocalcin, bone alkaline phosphatase) approving high turnover osteoporosis,

– the age of the patients 45–75 years.

All the patients have sufferred a chronic backache, showed less activity and were on regular medication with analgesics. 8 women had had a vertebral fracture, 5 women had had a proximal femur fracture and 2 women had had a wrist fracture in the past.

The patients received alendronate 1 tablet of 10 mg daily and 500 mg calcium per day oraly. They were encouraged to exercise after a course of physioterapy.

We performed a densitometry examination on HOLOGIC 2000 QDR at the onset of the study, after one year and after two years of treatment. We measured bone mineral density (BMD, bone mineral density, in g/cm^2), T score, Z score and change of the density in the lumbar spine (L1–L4 total value), in the neck region of the proximal femur (total value measured from the regions of the neck, greater trochanter, intertrochanteric region and Ward's triangle).

The T score is the difference between the BMD of the patient and the peak bone mass.

The Z score is the difference between the BMD of the patient and the mean values of density in the same age in the population.

Change – is a percentage change in density between two examinations of the same patient.

All patients answered a questionaire.

Results

Clinical results

One patient from 44 stopped the treatment because of dyspepsia and one because of abdominal distension. No patient complained of oesophagus iritation symptoms or of pyrosis. The compliance of alendronate was good in 42 women (95.5 %), who were able to continue on the treatment. 15 patients were very satisfied with the effect of the treatment, 22 were satisfied and 5 patients claimed not to be improved at the end of the study. A positive effect of the treatment was seen in 37 patients (88.1 %). 21 patients claimed to have no pain, 15 patients suffered a mild intermitent pain, 4 patients had a mild often pain and two patients had a moderate pain at the end of the two-year study. 24 patients used no analgesics, 9 patients used them irregularly, two patients used analgesics on and off and 7 patients used analgesics regularly after two years of treatment. 11 patients claimed to have normal activity, 22 patients had a very little diminished activity and 9 patients had a diminished activity in daily life. Movements of the spine were normal in 8 patients, mildly limited in 22 and moderately limited in 12 patients after two years of the treatment. We have encountered no symptomatic vertebral or nonvertebral fracture during the study (Tab. 1–5).

Bone densitometry results

The mean BMD in lumbar spine was improved in T score by 0.38 SD after one year and by 0.35 SD after the second year. The mean BMD improved in the neck region in T score by 0.21 SD after the first year and by 0.21 SD after the second year (Tab. 6).

The mean BMD in lumbar spine improved in Z score by 0.31 SD after one year and by 0.02 SD after the second year. The

Tab. 1. The patients' assesment.

	Number of patients	%
Excellent	15	35.7
Good	22	52.4
Not improved	5	11.9
Worse	0	0

The patients' assesment of the effect of the treatment was excellent or good in 37 patients (88.1 %), not improved in 5 (11.9 %).

Tab. 2. Pain before and after treatment.

	Before treatment		After treatment	
	n	%	n	%
No	0	0	21	50.0
Occasionally	3	7.1	15	35.8
Often, mild	12	28.6	4	9.4
Moderate	19	45.2	2	4.8
Severe	8	19.0	0	0

27 patients have had a moderate pain (64.2 %) before the treatment, but after the treatment only 2 patients had moderate pain (4.8 %). 21 patients had no pain after the treatment (50 %) and 19 patients (45.2 %) had a mild pain.

Tab. 3. Administration of analgesics.

	Before treatment		After treatment	
	n	%	n	%
No	0		24	57.2
Exeptionally	0		9	21.4
Occasionally	0		2	4.8
Often	9	21.4	3	7.1
Regularly	33	78.6	4	9.5

42 women used analgesics regularly before the treatment, only 7 women (16.6 %) used analgesics regularly after the treatment.

Tab. 4. Activity.

	Before treatment		After treatment	
	n	%	n	%
Normal	0	0	11	26.2
Mild limited	14	33.3	22	52.4
Marked limited	20	47.6	9	21.4
Minimal	8	19.1	0	0

The physical activity was markedly limited or minimal in 28 patients (66.7 %) before the treatment and in 9 patients (21.4 %) after the tratment. 11 patients had a normal physical activity (26.2 %) after the tratment.

Tab. 5. Mobility of the spine.

	Before treatment		After treatment	
	n	%	n	%
Normal	3	7.1	8	19.0
Mild limited	22	52.4	22	52.4
Marked limited	17	40.5	12	28.6

Mobility of the spine was markedly limited in 17 patients (40.5 %) before the treatment and in 12 (18.6 %) after the tratment.

mean BMD in the neck region improved Z score by 0.31 SD after the first year and by 0.16 SD after the second year (Tab. 7).

The mean change of bone mineral density in lumbar spine was +4.17 % after the first years and +4.19 % after the second year. We encountered increased BMD in the lumbar spine in 4.01 % or more in 22 patients after the first years and in the same number of patients after the second year. The mean change of bone mineral density in the femoral neck region was +4.46 % after the first years and +3.71 % after the second year. We encountered increased BMD in the neck of the femur of 4.01 % or more in 19 patients after the first years and in 20 patients after the second years (Tab. 8, 11).

All the data have been tested for the null hypothesis with student t-test (e.g. that the mean difference of bone density before and after the treatment is zero). According the student t-test all the data of the increased bone density in T score, Z score and change in lumbar and neck regions were statisticaly significant at the 5 % level of the significance ($p<0.05$) after the first and the second year of the study. The null hypothesis was refuted in all tests.

Tab. 6. The mean T-score.

	L spine	Hip
At the onset	-2.79	-2.51
After one year	-2.41	-2.30
After two years	-2.06	-2.09

There was an improvement of the T score in lumbar spine 0.38 SD after one year and 0.35 after the second year. There was an improvement of T score in proximal femur 0.21 SD after one year and 0.21 SD after the second year.

Tab. 7. The mean Z-score.

	L spine	Hip
At the onset	-1.12	-1.32
After one year	-0.81	-1.01
After two years	-0.79	-0.85

There was an improvement of the Z score in the lumbar spine by 0.31 SD after one year and 0.02 SD after the second year. There was an improvement of the Z score in the proximal femur 0.31 SD after one year and 0.16 SD after the second year.

Tab. 8. The mean percentage of change of bone density.

	L spine	Hip
After the first year	+4.17	+4.46
After the second year	+4.19	+3.71

There was an increase of bone density at the end of the first and the second years in both the vertebral and hip region.

The risk of a vertebral fracture (a threshold -2.51 SD in T score) has diminished in 13 patients of 30 (31 %) by the end of the study. The risk of a fracture of the neck of the femur (a threshold -2.51 SD in T score) was diminished in 14 patients of 30 (38 %) at the end of the study (Tab. 9, 10).

Discussion

Alendronate is a second generation bisphosphonate (aminobisphosphonates with the side chain ($(CH_2)_3 - NH_2$). Alendronate causes the inhibition of pharnesyl diphosphate synthetase and the production of mevalonate. It stops the production of prenylated proteins. It induces the apoptosis of osteoclasts and is specific to them. The effect of alendronate is an increase of mineralisation on the same volume of bone. In that way it increases the resistance of bone against fractures (10, 11).

The study proves the effect of alendronate 10 mg daily with calcium 500 mg per day supplementation for the treatment of postmenopausal osteoporosis. Currently we add to alendronate and calcium 800 IU of vitamin D per day oraly. The compliance was good in 42 from 44 patients (99.5 %). The quality of daily life has been improved in 37 of 42 patients (88.1 %). Moderate and severe pain was present in 27 patient (64.2 %) at the onset of the study and only in two patients (4.8 %) after two years of

Tab. 9. T-score in lumbar spine (L1-L4).

SD	At the onset n	After 2 years n
Over 0	0	3
0.0 till-1.0	3	5
-1.01 till-2.5	9	17
-2.51 till-3.0	13	11
-3.01 till-3.5	8	3
-3.51 till-4.0	5	1
-4.01 till-4.6	4	2

There were 30 patients at risk for pathological fractures according to T scores before treatment (71.4 %) and 17 (40.5 %) after two years therapy. The risk of the new fracture has decreased by 31 %.

Tab. 10. T-score in the proximal femur.

SD	At the onset n	After 2 years n
Over 0	0	0
0.0 till-1.0	2	8
-1.01 till-2.5	10	20
-2.51 till-3.0	14	7
-3.01 till-3.5	10	6
-3.51 till-4.0	2	0
-4.01 till-4.6	4	1

There were 30 patients at risk of pathological fracture of the proximal femur according T score before the treatment (71.4 %) and 14 (33.3 %) after two years of the treatment. The risk of a new fracture has decreased by 38 %.

treatment. Only 7 patients regularly used analgesics at the end of the study (initially all 44 patients used analgesics). The activity and movement of the spine has improved after two years.

BMD increased by 0.73 SD in the lumbar spine in T score after two years and 0.42 SD in the neck of the femur ($p<0.05$). BMD has increased by 0.33 SD in the lumbar spine in Z score after two years and 0.47 SD in the neck of the femur ($p<0.05$). The change of bone mineral density increased in the lumbar spine by +8.36 % ($p<0.05$) and in the neck of the femur by +8.17 % ($p<0.05$) after two years. There were no new symptomatic fractures during the study. The fracture risk of the vertebrae decreased by 31 % and the fracture risk in the proximal femur decreased by 38 %.

FIT study (2, 3) (Fracture Intervention Trial) assessed the effect of alendronate in 3 658 postmenopausal women after 3 years (alendronate n=1841, placebo n=1817). At the onset of the study all women had already one vertebral fracture or a T score of the proximal femur -2.5 SD or less. The mean age of the patients was 70.7 years. The risk of new vertebral fractures decreased by 47 % in the comparison to the placebo group and the risk of a fracture of the femoral neck decreased by 51 %. There was a reduction of symptomatic vertebral fractures by 59 % after 12 months and a reduction of the wrist fractures by 48 % after 3 years. 96 % of the women showed a favourable response to treatment after 3 years. The women with the highest increase of BMD have shown the lowest risk of a new vertebral fracture (9).

Tab. 10. T-score in the proximal femur.

Change in %	L1-L4 1st y n	L1-L4 2 y n	Hip 1st y n	Hip 2 y n
Less than-4	0	0	0	1
-2 till-4	0	2	2	1
0 till-1.99	7	2	4	3
0-2.0	5	1	4	3
2.01-4.0	8	15	13	14
4.01-6.0	13	11	12	11
6.01-8.0	2	7	2	6
8.01-10.0	4	2	1	2
10.01-12.0	1	1	1	0
12.01-14.0	1	1	1	1
14.01<	1	0	2	0

There was an increase of BMD in the lumbar spine at the end of the first year (4.01 %) and more in 22 patients (52.4 %) and in 22 patients at the end of the second year. There was an increase of BMD in the hip at the end of the first year (4.01 %) and more in 19 patients (45.2 %) and in 20 patients (47.6 %) at the end of the second year.

The FOSIT study (12) (Fosamax International Trial) is one year double blind study in 1908 postmenopausal women with low BMD. They were given alendronate 10 mg and calcium 500 mg daily. There was a progressive increase 5 % of BMD in lumbar spine. The incidence of nonvertebral fractures decreased by 47 % versus placebo group.

A two-year double blind multicentric study (4) has shown the therapeutical equivalance of alendronate 70 mg once weekly and 10 mg daily in the treatment of postmenopausal osteoporosis. The patients with alendronate 70 mg once weekly did not complain of a higher incidence of adverse effects in the comparison with alendronate 10 mg daily even in the day of administration (370 women with alendronate 10 mg, 519 women with alendronate 70 mg).

The mean change of vertebral BMD with alendronate 70 mg once weekly after 6 months was 3.3 % and with risedronate 5 mg daily was 2.5 %. The mean change of BMD in proximal femur with alendronate 70 mg once weekly after 6 months was 2.6 % and with risedronate 5 mg daily after 6 months was 1.0 % (13).

Tonino et al (14) have evaluated a favourable effect of alendronate in 350 postmenopausal women after 7 years in a placebo controlled study with 10 mg and 5 mg doses. There was an increase of BMD in the lumbar spine of 11.4 % with a 10 mg dose (8.2 % with 5 mg dose). There was a linear increase of BMD in lumbar spine 0.83 % per year with a 10 mg dose (0.6 % with 5 mg dose). The increase was statisticaly significant even in the sixth and seventh year of treatment. There was a continuous increase of BMD in proximal femur – at the end of the 7 years study in the greater trochanter at the mean of 9.5 % (5.6 % with 5 mg dose) and in the neck region 4.9 % (2.6 % with 5 mg dose). There was 64 % reduction of fracture risk in the spine after 7 years. They did not encounter an increase of resorption of bone mass in the subsequent two years after discontinuation of the treatment. The bone density did not change in the subsequent two years after discontinuation of the treatment The incidence of vertebral and nonvertebral fractures was

not higher in the two subsequent years after discontinuation of the treatment.

Cranney et al (7) compared the efficacy of antiporotic agents in large studies. There was a reduction of the risk of vertebral fractures with alendronate (8 studies, n=9360) 48 %, with residronate (5 studies, n=2604) 36 %, with raloxifen (one study, n=6828) 40 % and with calcitonin (one study, n=1108) 21 %. There was a reduction of the risk of nonvertebral fractures with alendronate (8 studies, n=8 603) 49 %, with risedronate (7 studies, n=12958) 27 %, with raloxifen (2 studies, n=6961) 9 % and with calcitonin (one study, n=1245) 20 %.

The meta-analysis of Cranney at al (6) of antiporotic agents showed that there was a continuous increase of BMD of the lumbar spine of 13.8 % after 10 years of the treatment with alendronate 10 mg daily. There was a continuous increase of BMD of the greater trochanter region of 10.7 % after 10 years of treatment with alendronate 10 mg daily. They emphasize the increase of BMD and the marked decrease of fracture risk.

Alendronate (Fosamax) has proven to be one of the most efficient agents in the treatment of postmenopausal osteoporosis. Among other antiosteoporotic agents it has the longest proven data from multicentric studies. Multicentric studies with alendronate show the highest increase of BMD in the vertebrae and in the peripheral skeleton. Alendronate therapy reduces the symptoms caused by osteoporosis. The big advantage of alendronate is that it is now administered once weekly. The compliance is very good and the incidence of adverse effects is very low. Therapy with alendronate gives the highest reduction of the risk of vertebral and nonvertebral fractures.

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