A Prospective Analytical Study of the Effects and Adverse Events of Alendronate (Aldren70®) Treatment in Thai Postmenopausal Women

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Objective: *To elucidate the efficacy and adverse events of alendronate (Aldren70®) after 12 months of treatment in 50 to 70 years old postmenopausal women.*

Material and Method: *The authors observed 50 postmenopausal women who had clinical conditions of osteopenia or osteoporosis and had never been treated with alendronate acid. Bone mineral density (BMD) of L1-L4, the left hip, and the left forearm were performed at the initial assessment and after 12 months of treatment. The serum levels of osteocalcin (OC), procollagen type 1 N-terminal propeptide (P1NP) and beta-crosslaps (beta-CTx) were performed at the baseline and then after 3 months, 6 months and 12 months of treatment. The data were analyzed using the SPSS software. Paired t-test was used to compare lumbar spine, hip and forearm before and after treatment.*

Results: *Treated by using Aldren70 once weekly for one year, the BMD of the lumbar spine increased highly up to 11.26% (g/cm^2) and 25.82% (T-score) from the base line ($p<0.001$ and $p<0.001$, respectively). On the other hand, the change in BMD of the left hip increased 17.54% (g/cm^2), 8.2% (T-score), at the left forearm increased 3.96% (g/cm^2), 7.62% (T-score) after 12 months respectively. There was significant increase of BMD between before and after 12 months. The mean values of bone markers at the 0.05 level before treatment, three months, six months, and 12 months of treatment in osteocalcin were 0.2813, 0.1242, 0.896, and 0.0889 ng/ml respectively. The P1NP were 36.1762, 19.3894, 14.3084, and 15.1260 ng/ml respectively. Beta-crosslaps were 0.2813, 0.1242, 0.0896, and 0.0889 ng/ml respectively. Adverse events found in five patients were the symptoms of stomachache (2, 4%), constipation/diarrhea (1, 2%), palpitation (1, 2%), and muscle/bone pain (1, 2%).*

Conclusion: *The generic alendronate (Aldren70) in our clinical trial was found to be highly effective at the spine concerning the bone mass improvement and less at the hip and wrist joints in comparison. All the result figures met the standard efficacy after 12 months follow-up by increasing bone mass and reducing serum bone markers.*

Keywords: *Alendronate, Osteoporosis, BMD, Bone Markers, Menopause*

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The main pharmacological effect of alendronic acid to bone is to inhibit the osteoclastic action and allow osteoblastic cell to carry on the natural activity[1]. It increases bone mass and reduces bone markers in osteoporotic patients[2-5]. After the patent of Fosamax 70 mg tablet with the Food and Drug Administration (FDA) expired, FDA approved generic versions of Fosamax on February 6, 2008 to Teva Pharmaceuticals and Barr Laboratories, USA to manufacture the 70-mg, once-weekly. There were many generic competitors launch their product in the market. For the original alendronic acid product (Fosamax, MSD), there was no question regarding the pharmacological effect or clinical outcome for both short-term and long-term use[6-13] including the efficacy in osteoporosis with other conditions[14-20], and some of the untoward effect[21-24]. Aldren70 was a generic alendronic acid one made in Poland and launched into Thailand. Problems of many generic drugs are unacceptability about the efficacy and its complications from the users. Standardization of the generic drug manufacturing was in doubt because there was no proof or evaluation in detail of the drugs. There was no evidence whether bioavailability and bioequivalence in the blood serum were equal to the original one[25]. In addition, what was the clinical efficacy and cost effectiveness?[26]. To prove the clinical outcome of the generic alendronate (Aldren70), the present team had submitted the research project for review and got approval from the Ethics Committee and the Orthopedics Department, X-ray Department

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and Biochemistry Department, Faculty of Medicine, King Chulalongkorn University, Bangkok, Thailand. Osteoporosis is a common health problem of elderly women in postmenopasual states that increase bone fractures and mortality rates due to decrease of bone strength[27]. The current therapeutic goal of anti-resorptive agents is to stop further loss of bone mineral density (BMD) and to prevent bone fractures in order to enhance the quality of life.

Moreover, the bone markers levels should be interpreted carefully by using an appropriate reference range because of its significance. The introduction of reliable, specific test for the biochemical markers of the bone metabolism would help the clinical management of metabolic bone diseases, including osteoporosis. There are three types of bone markers that were analyzed in the present study. First, Osteocalcin, also known as bone Gla protein, is a marker of bone formation. It is vitamin K and vitamin D-dependent protein produced by osteoblast and is the most abundant and most widely studied as the non-collagenous proteins in bone[28]. Second, Procollagen type I N propeptide (P1NP) is a marker of early bone formation, generally appears during osteoblast proliferation, and produces during the formation of type I collagen. This is the most sensitive marker for follow-up after hormonal treatment in menopausal women[7,29]. The last one is β-crosslaps (Beta-CTx), a helical protein that is cross-linked with both the C-terminal and N-terminal ends of the molecule. A fragment of collagen at its C-terminal end changes its nature as bones ageing, whereby its constituent alpha form of aspartic acid converts to the beta one. The fragment or telopeptide was called Beta-CTx, which is a specific marker for the degradation of Type I collagen. During bone resorption, proteases degrade collagen, and Beta-CTx is released into the circulation. Increased levels of Beta-CTx was found in serum in state of increased bone resorption and may return to normal levels during inhibiting bone resorption therapy[30,31].

The purpose of the present study is to determine effects and safety of alendronate 70 mg (Aldren70) treatment by comparing the results between before and one year after treatment in osteoporosis patients who participated in the study.

Material and Method

Study population

We studied 50 postmenopausal women aged 50 to 70 years old in Thailand. The data were collected between December 2010 and December 2011. At first, 60 women were recruited in the study, of whom 50 women met the criteria. The patients were selected according to the following inclusion criteria: patients with no menstruation for more than 12 months and having the BMD at the lumbar spine, hip, forearm of a T-Score less than -2.5, the women never received alendronate, bisphosphonate or any other medicine for bone maintenance. All participants were asked to give written informed consent before enrolled in the study. The present study protocol was approved by the Ethics Committee of Faculty of Medicine, King Chulalongkorn Hospital.

Measurements of bone mineral density

The bone mineral density of the lumbar spine, hip, forearm was measured by Dual energy X-ray Absoptiometer (DXA) in the anteroposterior view (Department of Imaging Center, Chulalongkorn hospital) to determine subjects' eligibility on the basis of their bone mineral density T score.

Measurements of biochemical bone markers

All patients were measured serum Osteocalcin, P1NP, beta-crosslaps. The patients fast blood for eight hours: ten milliliters of fasting blood was collected between 8.00 and 9.00 am, starting at baseline, three months, six months, and 12 months of the treatment. In addition, an overall safety assessment was made by considering laboratory data and adverse effects. The symptoms related to the adverse effects of the treatment were detected by observing by patient's reports in each visit. Bone markers were measured by the Electrochemiluminescence immunoassay (ECLIA).

Statistical analysis

The data were analyzed by using SPSS software version 12.0. Clinical characteristics of patients were presented as mean ± SD. Paired t-test was used to compare lumbar spine, hip and forearm before and after treatment. A *p*-value less than 0.05 was considered as statistically significant.

Results

The clinical characteristics of the 50 patients: they had clinical conditions of osteopenia or osteoporosis. The postmenopausal women enrolled age was between 50 to 70 years old, mean age of 65.66±7.64, mean height (cm) of 152.68 and BMI of 23.8 kg/m².

The results showed that bone mineral density (BMD) of the lumbar spine L1-L4 was highly improved 1 year after treatment. The lumbar spine significantly increased up to 11.26% (g/cm^2) (p-value <0.001) and T-score at the lumbar spine increased 25.82% (p-value <0.001) from the baseline after 1 year. The statistical analysis of the T-score at the lumbar spine L1-L4 after 12 months treatment revealed significant change with paired t-test as shown in Table1.

On the other hand, changing in BMD of hip increased 17.54% (g/cm^2) and T-score increased 8.2% (p-value <0.001) as shown in Table 2. At the forearm the increase was 3.96% (g/cm^2) and T-Score increased 7.62% (p-value <0.001) as shown in Table 3, after one year respectively. Therefore, the mean value of BMD after receiving medication increased higher at lumbar spine.

The mean value of serum Osteocalcin decreased after treatment for three months and decreased rapidly between three and six months and after six months, the mean value had increased slowly until 12 months. Significant changes in these levels during the study period were shown in Fig. 1.

The mean value of Procollagen type 1N-terminal propeptide (P1NP) decreased rapidly after treatment for three months and decreased slowly between three and six months and after six months, the mean value increased slowly until 12 months, as shown in Fig. 2.

The mean value of Beta-crosslaps decreased rapidly after treatment for three months and decreased slowly between three and six months and after six months, the mean value had increased slowly until 12 months, as shown in Fig. 3.

Table 1. Comparison of the lumbar spine between before and after treatment using Aldren70 for 12 months

Characteristic	n	Mean score (g/cm^2)		% changes	p-value	Mean score (T-score)				% changes	p-value
		Pre-treatment	Post-treatment			Pre-treatment	Post-treatment	Standard deviation			
								Before	After		
L1	50	0.7490	0.8277	11.05	<0.001	-2.1128	-1.6362	1.12	1.08	22.56	<0.001
L2	50	0.7964	0.8712	10.94	<0.001	-1.7556	-1.4689	1.24	1.29	16.33	<0.001
L3	50	0.8048	0.9226	13.55	<0.001	-1.9457	-1.3282	1.20	1.38	31.73	<0.001
L4	50	0.8125	0.9265	11.40	<0.001	-2.3833	-1.2238	1.55	1.63	41.26	<0.001
L1-L4	50	0.7890	0.8887	11.26	<0.001	-2.5735	-1.3898	1.18	1.28	25.82	<0.001

Table 2. Comparison of the hip between before and after treatment using Aldren70 for 12 months

Characteristic	n	Mean score (g/cm^2)		% changes	p-value	Mean score (T-score)				% changes	p-value
		Pre-treatment	Post-treatment			Pre-treatment	Post-treatment	Standard deviation			
								Before	After		
Neck	50	0.6034	0.6604	9.45	<0.001	-2.174	-1.734	0.65	1.01	20.00	<0.001
Troch	50	0.5433	0.5850	7.68	<0.001	-1.1612	-1.0551	0.75	0.82	09.14	0.031
Inter	50	0.8029	0.8439	5.11	<0.001	-1.246	-0.8902	0.81	0.84	26.71	<0.001
Ward's	50	0.7006	0.7493	6.95	<0.001	-2.4095	-2.2119	0.93	1.02	12.42	0.027
Total	50	0.4442	0.5221	17.54	<0.001	-2.5095	-1.4388	0.92	1.00	8.20	0.007

Table 3. Comparison of the forearm between before and after treatment using Aldren70 for 12 months

Characteristic	n	Mean score (g/cm^2)		% changes	p-value	Mean score (T-score)				% changes	p-value
		Pre-treatment	Post-treatment			Pre-treatment	Post-treatment	Standard deviation			
								Before	After		
UD	50	0.3096	0.3176	2.58	0.236	-2.1375	-1.9650	1.29	1.39	9.41	0.004
Mid	50	0.4793	0.5079	5.97	0.003	-2.1594	-2.0031	1.42	1.35	7.68	0.014
1/3	50	0.5327	0.5644	5.95	0.480	-2.2844	-1.9800	1.45	1.29	9.36	0.003
Total	50	0.4391	0.4565	3.96	0.005	-2.5326	-2.3822	1.48	1.41	7.62	0.028

UD = ultradistal

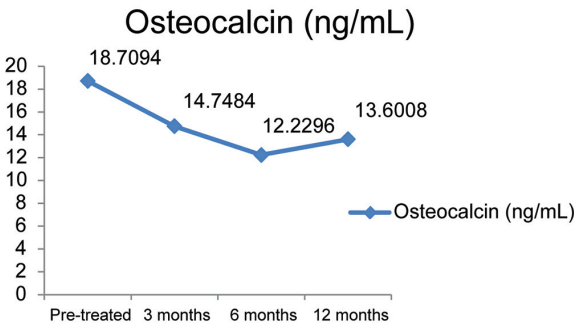

Fig. 1 Results of mean value of Osteocalcin before and after 1 year, showed significant change level during the study period. The mean values of osteocalcin were decreased after treatment 3 months and decreased highly at 3-6 months and after 6 months, the mean value had increased slowly until to 12 months thus 18.71, 14.72, 12.23 and 13.60 respectively, there were significant changed in these level during the study period.

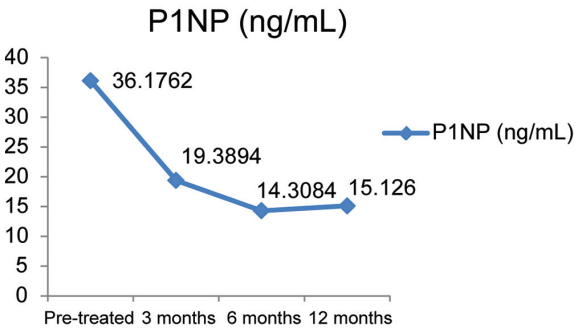

Fig. 2 Results of mean value of P1NP before and after 1 year, showed significant change level during the study period.The mean values were decreased highly after treatment 3 months and decreased slowly at 3-6 months and after 6 months, the mean value had increased slowly until to 12 months.

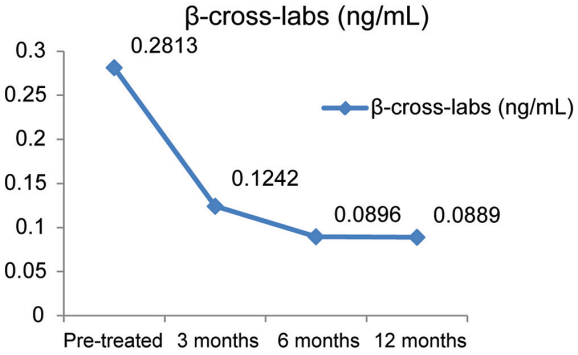

Fig. 3 Results of mean value of beta-cross laps before and after 1 year, showed significant change level during the study period. The mean value of were decreased highly after treatment 3 months and decreased slowly at 3-6 months and after 6 months, the mean value had increased slowly until to 12 months.

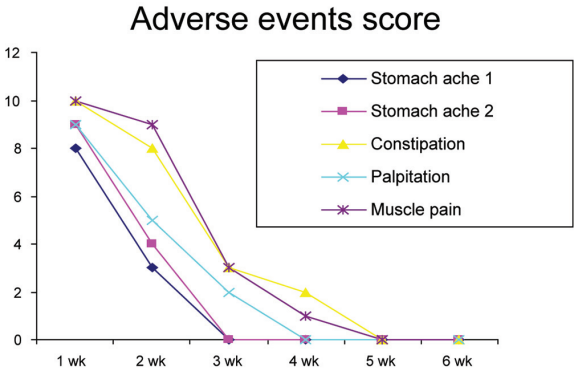

Fig. 4 Adverse event effects.

Adverse events

Safety analysis was performed on the 50 patients. Adverse events were evaluated based on the occurrence of clinical symptoms and biochemical data for the incidence of adverse effects, there were four minor symptoms with five patients. Clinical symptoms included stomachache (2 cases) that disappeared after three weeks, constipation (1 case) that disappeared after one month, palpitation (1 case) that disappeared after three weeks, and muscle pain (1 case) that disappeared after one month, respectively (Fig. 4).

One subject was discarded from the study due to her intolerance of the drug after taking for one and a half months. This patient developed severe nausea, vomiting, and bone pain every time and last for several days after taking the pill. The problems disappeared after stop taking pills. There were five cases with minor complications but could tolerate well after six weeks.

Discussion

The present study was conducted by a team of doctors, a researcher, and a statistical analyst. Each worked individually: doctors performed the clinical evaluation, the researcher did the data collection and the statistical analysis. At the end of the project, doctors summed up the outcome and reported results. As mentioned earlier, most generic drugs have the user trust problem about the efficacy because there are no proven data. Although the sale price of generic Aldren70 for one year in Thailand is approximately

US$ 400, it is cheaper than the original one. However, there were many concerns about quality, efficacy, standardization of manufacturing process, contamination, bioavailability, bioequivalence, desirable length in taking it, and adverse drug reaction. In the present research, we proved that the generic alendronate sodium (Aldren70) met the same level of standard pharmaco-therapeutic efficacy as the original alendronate sodium, and did far better efficacy definitely seen at the spines. The T-score improvement at the spine was 25.82% on average. The hip and wrist joints also showed the T-score improving after taking the pill for one year. All the figures of serum bone marker definitely decreased at three months follow-up compared to pre-drug taking and continued to decrease to nearly peak at six months. After that, the serum bone marker decreasing was slowed down at 1-year follow-up. The result was the same as the original alendronate sodium. Regarding the side effect, Aldren70 had minor adverse drug reaction in six of the 50 subjects. Only one subject could not tolerate the drug and was removed from the research project. The adverse drug reaction was not so serious (nausea, vomiting, and bone pain). The five subjects had simple drug reactions and the symptom disappeared after four weeks. At present, the second year clinical trial is still going on, and the results will be later reported. The aim is to follow-up the efficacy of continuing using Aldren70 to prevent fractures in our project[27]. There was no fracture occurring during the one-year study.

Conclusion

The generic alendronate (Aldren70) in the present clinical trial was found to be highly effective on the spine concerning the bone mass improvement, but less at the hip and wrist joints when compared to each other. All the result figures met the standard efficacy after one-year follow-up, by increasing bone mass and reducing serum bone marker.

What is already known on this topic?

The main pharmacologic effect of alendronic acid bone is to inhibit the osteoclastic action and allow osteoblastic cell to carry on the natural activity. It increases bone mass and reduces bone markers in osteoporotic patients.

After the patent with the FDA for Fosamax 70 mg tablets expired, the FDA approved generic versions of fosamax 70 mg on February 6, 2008 to Teva Pharmaceuticals and Barr Laboratories USA to manufacture for Fosamax 70 mg tablets (once weekly). There were many generic competitors launching their products into the market. For the original alendronaic acid product (Fosamax 70 mg, MSD), there were no problem regarding to the pharmacologic effect or clinical outcome both for short and long term using including the efficacy in osteoporosis with other conditions. Aldren70 was a generic alendronic acid one made in India and launched into Thailand. Problems of many generic drugs were unaccepted about the efficacy and its complications from their users. Standardization of the generic drug manufacturing was in doubt because there was no proof or evaluation in detail of the drugs. There was no evidence whether bioavailability and Bioequivalence in the blood serum were equal to the original one. Furthermore, what was the clinical efficacy and cost effectiveness?

To prove the clinical outcome of the generic Alendronate (Aldren70), our team pursued the research project under the permission of Ethic Committee, Department of Orthopedic, Department of X-ray and Department of Biochemistry, Faculty of Medicine, King Chulalongkorn University, Bangkok, Thailand.

What this study adds?

Although the sale price cost of generic Aldren70 for one year in Thailand was approximately US$ 400, it was much cheaper than the original one. However, there were many questions of the drug concerning about quality, efficacy, standardization of manufacturing process, contamination, bioavailability, bioequivalence, desirable length in taking it, and adverse drug reaction.

In the present study, we proved that the generic alendronic acid (Aldren70) met the same level of standard pharmaco-therapeutic efficacy as the original alendronic acid. The best result was definitely seen at the spine. The T-score improvement at the spine was 28.82% on average. The hip and wrist joints also showed the T-score improving after taking the pill for one year. All the figures of serum, bone markers were definitely decreasing at three months follow-up compared to pre-drug taking and continued decreasing to nearly peak at six months. After that, the serum bone markers decreasing was slowed down until one-year follow-up. These result figures were the same as the original alendronic acid. Regarding the side effect, Aldren70 had minor adverse drug reactions. The adverse drug reaction was not so serious (nausea, vomiting, and bone pain). At present, the second year clinical trial is still going on and the results will be reported later. There were no fractures occurring

during our one-year project study. The generic alendronic acid (Aldren70) in our clinical trial was found to be highly effective at the spine concerning the bone mass improvement and less at the hip and wrist joints when compared to each other.

All the result figures met the standard of efficacy after one-year follow-up by increasing bone mass and reducing serum bone marker.

Potential conflicts of interest

None.

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การศึกษาเพื่อประเมินประสิทธิภาพความปลอดภัยและเหตุการณ์ไม่พึงประสงค์ของยา alendronate (Aldren 70®) ในการรักษาสตรีไทยวัยหมดประจำเดือนที่มีภาวะของโรคกระดูกพรุน

ประกิต เทียนบุญ, นรา จารุวังสันติ

วัตถุประสงค์: เพื่ออธิบายชี้แจงให้เห็นถึงประสิทธิภาพความปลอดภัยและเหตุการณ์ไม่พึงประสงค์หลังจากได้รับยาอเลนโดรเนต (อัลเดรน 70) เป็นระยะเวลา 12 เดือน ในสตรีวัยหมดประจำเดือน ช่วงอายุ 50 ถึง 70 ปี

วัสดุและวิธีการ: ผู้นิพนธ์ได้ศึกษาผู้ป่วยสตรีวัยหมดประจำเดือนที่มีภาวะของโรคกระดูกบางไปจนถึงกระดูกพรุนและไม่เคยได้รับยาอเลนโดรเนตมาก่อน วัดผลการรักษาโดยใช้ BMD ก่อนและหลังรับประทานยา ตรวจวัดประเมินการตอบสนองของการใช้ยามีการเปลี่ยนแปลงการสร้างและสลายกระดูกจากผลเลือดโดยใช้ biochemical bone markers (serum osteocalcin, procollagen type 1-N-propeptide (P1NP), serum β-Crosslaps (β-CTx)) ในช่วงระยะก่อนทาน 3 เดือน, 6 เดือน และ 12 เดือน วิเคราะห์ข้อมูลทางสถิติโดยใช้ โปรแกรมสำเร็จรูป SPSS เปรียบเทียบผลการรักษาก่อนรับประทาน-หลังรับประทานโดยใช้ paired t-test วิเคราะห์การเปลี่ยนแปลงจากเดิมที่ระดับความเชื่อมั่น 95%

ผลการศึกษา: พบว่าสามารถเพิ่มมวลกระดูกในส่วนเอวหลังจากรับประทานยา 1 ปี อย่างเห็นได้ชัดจากค่า BMD (g/cm^2) และ BMD (T-score) 11.26%, 25.82% ตามลำดับ ส่วนข้อสะโพกมีการเปลี่ยนแปลงของมวลกระดูกเพิ่มขึ้นของค่า BMD (g/cm^2) และ BMD (T-score) 17.54%, 8.2% ตามลำดับ และส่วนข้อมือมีการเปลี่ยนแปลงของมวลกระดูกของค่า BMD (g/cm^2) และ BMD (T-score) 3.96%, 7.62% ตามลำดับ และทุกส่วนมีการเปลี่ยนแปลงจากเดิมเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติที่ระดับความเชื่อมั่น 95% ($p<0.05$) และสำหรับการประเมินแนมโน้มการเปลี่ยนแปลงของผลเลือดในระยะก่อนรับประทาน 3 เดือน, 6 เดือน และ 1 ปี ได้ผลการเปลี่ยนแปลงดังนี้ ผลเลือดของค่า mean osteocalcin (0.2813, 0.1242, 0.896 และ 0.0889 ng/ml) ผลเลือดของค่า mean P1NP (36.1762, 19.3894, 14.3084 และ 15.1260 ng/ml) และผลเลือดของค่า mean β-Crosslaps (0.2813, 0.1242, 0.0896 และ 0.0889) ตามลำดับ อาการไม่พึงประสงค์มี 5 ราย คือ ปวดท้อง 2 ราย คิดเป็น 4%, อาการท้องผูกหรือท้องเสีย 1 ราย คิดเป็น 2%, อาการใจสั่น 1 ราย คิดเป็น 2% และปวดกล้ามเนื้อและกระดูก 1 ราย คิดเป็น 2%

สรุป: การใช้ยาสามัญอเลนโดรเนต (อัลเดรน 70) ให้ผลการรักษาในระดับสูงและเห็นผลชัดเจนในส่วนของกระดูกสันหลังส่วนเอว นอกจากนั้นยังให้ผลต่อข้อสะโพกและข้อมือด้วยเช่นกัน โดยยืนยันผลการรักษาของยาจากการตรวจวัดโบนมาร์คเกอร์ ซึ่งผลของค่าดังกล่าวมีการสร้างและสลายมวลกระดูก ซึ่งสามารถตรวจสอบได้ชัดเจนว่ามีการตอบสนองของยาอัลเดรน 70 ในระหว่างการรักษา