ADHERENCE TO BISPHOSPHONATE THERAPY IN POSTMENOPAUSAL OSTEOPOROTIC WOMEN

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ABSTRACT

INTRODUCTION: Osteoporosis is a metabolic bone disease caused by a decrease in the bone mineral density. It is a major public health threat as it weakens bones, especially those in the wrist, spine, or hip, and causes them to break easily.

AIM: The study aimed to find how strictly postmenopausal women with osteoporosis adhere to a long-term therapy with bisphosphonates.

PATIENTS AND METHODS: The study was conducted over a 24-month period. It included a total of 341 randomized patients with postmenopausal osteoporosis; the diagnosis was made on the basis of clinical and radiological evidence and a DXA T-score of the axial skeleton and the left hip less than -2.5 SD. Therapy included per os administration of alendronate 70 mg once a week or 50 mg of ibandronate once a month.

RESULTS: The patient medication persistence at the end of month 12 was 86.80%, and at the end of month 24 month – 58.94%. The medication possession ratio (MPR) in the bisphosphonate therapy at 6, 12, 18, and 24 months varied from 0.93 to 1.00. This suggests that there was a very good patient medication adherence of the study subjects to the 24-month treatment with bisphosphonates. The patient medication persistence dropped significantly at the end of month 12.

CONCLUSION: Compliance of patients with antiresorptive therapy depends on the specific socio-economic conditions and the attending physician’s behaviour. Very rarely, treatment is discontinued because of adverse effects exerted by the drugs or because patients may not be convinced that they have osteoporosis.

Key words: osteoporosis, bisphosphonate, persistence, adherence, osteoporotic women

INTRODUCTION

Osteoporosis is a metabolic bone disease induced by a decrease in bone mineral density (BMD). The condition increases significantly the risk patients run of sustaining fractures of the spine, hip, wrist and other bones. Osteoporosis is one of the major problems of public health. Timely treatment of this disease is key to reducing bone destruction, increasing bone strength and bone density and minimising fracture risk. A long-term, systematic treatment is absolutely necessary in postmenopausal osteoporosis. Bisphosphonates (alendronate, risedronate, ibandronate) are agents that inhibit the osteoclast-induced bone resorption, suppress bone metabolism and reduce fracture risk. In treating oligo-symptomatic chronic diseases such as postmenopausal osteoporosis, many patients are often not compliant enough to the therapy they have been prescribed to receive. According to literature sources, 45 to 55% of patients with chronic diseases such as hypertension, gout, hyperlipidemia and atherosclerosis cease therapy earlier than they should. Women with osteoporosis undergoing systematic therapy vary widely in number from country to country, the therapeutic time often being suboptimal. Kothawala reports that more than 50% of osteoporosis patients treated with bisphosphonates adhere poorly to the prescribed treatment regimen and discontinue treatment within 6 or 12 months of initiation. In small groups of patients persistence and adherence to the prescribed anti-resorptive therapy reaches 60-80%. The willingness of patients with osteoporosis to undergo long-term treatment depends on the concomitant diseases, the number of hospitalizations related to other diseases, previous fractures, and the changes in BMD. Poor adherence to treatment could sometimes be associated with insufficient efforts on the part of the doctors to make patients overcome the negative attitude to the treatment. Some of the patients resume anti-
osteoporosis therapy after adequate intervention by a specialist.

AIM

The study aimed to assess the adherence of postmenopausal women with osteoporosis to a long-term treatment with bisphosphonates. Also the factors limiting the implementation of prescribed treatment with bisphosphonates were analyzed.

PATIENTS AND METHODS

Screening criteria were met by 490 women with postmenopausal osteoporosis who were past 55 years of age. Of these, 341 were randomized. Written informed consent was obtained from all of these subjects for participation in the study. The study was conducted over a 24-month period (2005 – 2009). The diagnosis of postmenopausal osteoporosis was based on clinical and radiological evidence and on dual-emission X-ray absorptiometry (DXA) of axial skeleton and left hip. The study included patients with a T-score lower than -2.5 SD. The diagnosis of postmenopausal osteoporosis met the requirements of internationally accepted criteria.4 Randomized women received per os treatment with 70 mg alendronate once a week or ibandronate 50 mg once a month. Exclusion criteria were discontinuation of prescribed therapy or contraindications to the bisphosphonates therapy. Women on a regular hormone treatment were not randomized. Patients who discontinued treatment for more 60 days dropped out of the study. Control clinical examinations were performed every 6 months. The regularity of reception of the prescribed anti-osteoporosis medications was checked through patients self-reporting. Concomitant diseases and the associated medications were also registered. Monitoring of patients with hypercalciuria and hyperphosphaturia was focused on diagnosis. The study included women with medium or low personal income - from BGN 150 to ~ BGN 1000 a month (75-500 Euros).

Comorbid prevalence included an average of 2 comorbidities. Over the study period the number of hospitalizations for diseases unrelated to osteoporosis was 16.

The randomised patients were completely supplied with bisphosphonate by the Health Insurance Fund. Under current rules, the patients paid some of the cost of the bisphosphonate. Changing medications (from alendronate to ibandronate or vice versa) did not exclude the patient from the study. Verification of the received treatment was done by means of the health insurance prescription book. Monitoring included drug tolerance to the administered anti-resorption therapy, the BMD score, and the number of fractures before and after initiation of treatment.

Age distribution of the studied women with osteoporosis is presented in Table 1.

Three parameters were used in assessing the regularity of reception of the prescribed anti-osteoporosis medications: compliance, persistence, and adherence. The definitions of these three parameters do not overlap completely in different literary sources.5,12 For consistency purposes of our results with those of other authors we cite here the basic definitions of the variables we used and which comply with the requirements of the American College of Rheumatology – ACR.11

Patient medication compliance: the extent to which a patient acts in accordance with the prescribed recommendations made by the provider with respect to timing, dosage, and frequency of medication taking. “Compliance” can also be considered in a more general aspect to include details of how the medication is taken - with water, lemonade, coffee, milk, etc. This study used “self reported compliance” recording the patients’ self-reported data about the specific manner of administering the therapy.13,14

Patient medication persistence: how long and adequate the anti-osteoporosis therapy has been and whether the patient has received the therapy as long as it has been recommended. “Medication persistence” is measured by the time from commencement to completion of the prescribed treatment compared with the periods during which treatment is actually administered.

Patient medication adherence to the prescribed therapy. According to the definition of the International Society For Pharmacoeconomics and Outcomes Research-ISPOR (July 2008), this is a summarizing variable, the sum of the medication compliance and medication persistence. To measure patient medical adherence we used the medication possession ratio (MPR), a method also often used for prolonged medical treatment in other diseases.8,15,16 MPR is calculated as the number of days during which the patient actually received the prescribed therapy divided by the number of days of the therapeutic term.

STATISTICAL ANALYSIS

In the study we calculated 95% confidence interval (CI) of patient medication persistence, and used the
dynamic changes analysis and a graphical analysis of the current combination at equal time intervals. Medication possession ratio was used to measure the adherence of patients to regular therapy. The MPR index was calculated separately for each one-month period.

RESULTS

Distribution by age/number of observed women with osteoporosis is presented in Table 1.

Our results on persistence (the duration of reception of prescribed therapy) for alendronat or risedronat per month is presented in Table 2.

Table 3 presents the results on patient medication persistence to antiresorptive therapy at 6, 12, 18 and 24 months in the studied postmenopausal women.

In assessing the patient medication persistence to the recommended therapy of 341 patients with postmenopausal osteoporosis, 45 patients (13.20%) discontinued treatment with bisphosphonates at the end of month 12, while 296 patients (86.80%) continued treatment. At the end of the month 24 the total number of women who discontinued treatment increased to 140 (41.06%) as 201 (58.94%) women continued their treatment for 24 months. Interruption of therapy is most often seen at the end of 6, 12 and 18 months. We relate this dynamics to the fact that the renewal of documents to obtain subsidized health insurance fund drugs is carried out at the end of each 6 months.

The patient medication adherence to the bisphosphonates therapy in the randomized 341 women was calculated using MPR, and the method applied was “analysis of dynamic changes” (Table 4).

Table 4 presents the data for the MPR monthly dynamics for the patient medication adherence of women who received the bisphosphonate therapy for 24 months without ceasing it. For the different months of study values fluctuate from 0.93 to 1.00. A high degree of patient medication adherence to the prescribed treatment of patients was established.

Table 1. Distribution by age/number of randomized women with postmenopausal osteoporosis

<table>
<thead>
<tr>
<th>Age</th>
<th>55 - 59</th>
<th>60 - 64</th>
<th>65 - 69</th>
<th>≥ 70</th>
<th>Mean (SD), years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>84 (24.6%)</td>
<td>81 (23.7%)</td>
<td>66 (19.4%)</td>
<td>110 (32.3%)</td>
<td>64.7 (SD 8.4)</td>
</tr>
</tbody>
</table>

Table 2. Patient medication persistence for alendronat or risedronat

<table>
<thead>
<tr>
<th>Months</th>
<th>Dropped out patients (y*)</th>
<th>Months</th>
<th>Dropped out patients (y*)</th>
<th>Months</th>
<th>Dropped out patients (y*)</th>
<th>Months</th>
<th>Dropped out patients (y*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>7</td>
<td>5</td>
<td>13</td>
<td>16</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>8</td>
<td>2</td>
<td>14</td>
<td>8</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>9</td>
<td>4</td>
<td>15</td>
<td>6</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>10</td>
<td>3</td>
<td>16</td>
<td>9</td>
<td>22</td>
<td>5</td>
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<tr>
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<td>1</td>
<td>11</td>
<td>4</td>
<td>17</td>
<td>5</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>12</td>
<td>12</td>
<td>18</td>
<td>11</td>
<td>24</td>
<td>13</td>
</tr>
</tbody>
</table>

* (y) - absolute number of patients treated at the end of the respective month.

Table 3. Patient medication persistence of postmenopausal women to antiresorptive therapy at 6, 12, 18 and 24 months

<table>
<thead>
<tr>
<th>Months</th>
<th>Dropped out patients (n) every 6 months</th>
<th>Patients in treatment (n/%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>5</td>
<td>326</td>
<td>95.60%</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>296</td>
<td>86.80%</td>
</tr>
<tr>
<td>18</td>
<td>55</td>
<td>241</td>
<td>70.67%</td>
</tr>
<tr>
<td>24</td>
<td>40</td>
<td>201</td>
<td>58.94%</td>
</tr>
</tbody>
</table>
Women who discontinued treatment during the follow-up intervals for 60 days or more dropped out from the calculations.

Fig. 1 presents the dynamic changes of MPR per months. They fluctuate around a straight horizontal line parallel to the abscissa. This feature of the dynamics of the values of MPR is to support the existence of statistical reliability of the results and the adequacy of the volume of the studied sample.

During the study period two cases of fractures were observed - one of the radius and one of the humerus.

In 9 patients therapy was discontinued because of side effects of bisphosphonates.

**DISCUSSION**

Strict adherence to recommended therapy presents a real challenge for patients with postmenopausal osteoporosis. The therapy’s success is essentially dependent on the medication effectiveness and the behaviour of treated patients. Our results indicate that 13.20% of the patients discontinued bisphosphonates treatment at the end of the first year, this percentage reaching 41.06% at the end of the second year. This poor adherence to bisphosphonate treatment has been established in nonrandomized women with postmenopausal osteoporosis. As much as 45% of the patients have been reported to cease anti-osteoporosis therapy at the end of the

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**Table 4. Analysis of dynamic changes in MPR to treatment with bisphosphonates at 6, 12, 18, 24 months in women taking the drug continuously for 2 years**

<table>
<thead>
<tr>
<th>Month</th>
<th>Patients total monthly (y)</th>
<th>Patients total</th>
<th>Days in the month</th>
<th>Real Days</th>
<th>Theoretically days with therapy (t)</th>
<th>Medication possession ratio (MPR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>341</td>
<td>341.0</td>
<td>31</td>
<td>10371</td>
<td>10571</td>
<td>1.00</td>
</tr>
<tr>
<td>6</td>
<td>326</td>
<td>317.1</td>
<td>30</td>
<td>9514</td>
<td>9780</td>
<td>0.97</td>
</tr>
<tr>
<td>12</td>
<td>296</td>
<td>278.2</td>
<td>31</td>
<td>8623</td>
<td>9176</td>
<td>0.93</td>
</tr>
<tr>
<td>18</td>
<td>241</td>
<td>236.1</td>
<td>30</td>
<td>7083</td>
<td>7230</td>
<td>0.97</td>
</tr>
<tr>
<td>24</td>
<td>201</td>
<td>198.1</td>
<td>31</td>
<td>6140</td>
<td>6231</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Column 2: total number of patients receiving bisphosphonates by months (y)  
Column 3: actual number of patients relative to baseline  
Column 4: number of days in the respective months  
Column 5: actual number of days of treatment with bisphosphonates  
Column 6: theoretical number of days with adequate treatment in months  
Column 7: MPR index by months.

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**Figure 1.** Graphical analysis of dynamic monthly changes in patient medication adherence to bisphosphonates therapy in postmenopausal women.
first year after initiating it. Other authors report a higher percentage, 57.5%, The average adherence rate is said to be 75%, ranging from 4.6% to 100%. There have been reports that 52%-56% of all patients continue treatment with bisphosphonates even beyond 5 years. In a large study of “self-reporting” women over 45, seven months after initiation of treatment 70% of study subjects were found to have strictly adhered to the osteoporosis medication. The causes and circumstances related to compliance to bisphosphonates are complex and difficult to define. Compliance of patients to receive an antiresorptive therapy depends on the socio-economic conditions, on the health insurance system and the behaviour of the attending physician. The price of antiresorptive drugs is also a major factor. It is well known that a low bone density found by DXA is not the ideal method for predicting fracture risk. According to literature data DXA can predict less than half of the cases in which there will be post-osteoporotic fractures. It is also possible that some of the low BMD patients included in our study do not have osteoporosis. Discontinuation of therapy is rarely associated with the presence of side effects of the administered drug, or lack of belief in patients that they have osteoporosis (3.1%). Usually this refers to patients with limited intelligence, poor education or because of the fact that younger women cannot accept the fact that they have osteoporosis. Discontinuation of therapy may be due to a lack of positive dynamics in the control of bone density measurements (0.5%). Few patients and physicians change therapy or interrupt it because they think that the disease is refractory. Some of the patients are poorly informed about the duration of antiresorptive therapy and, as a consequence often cease treatment after the sixth month. Not infrequently it is economic reasons that determine the compliance and persistence of treatment (19.3%). It is quite erroneous to qualify patients as noncompliant, actually they should be considered misscompliant. Adherence to anti-osteoporosis treatment in women decreases at over 80 years of age. It is a very rare case that patients or doctors cease the antiresorptive therapy for no good reasons, for fear of the side effects of the drugs. Studying adherence to treatment is of great practical and scientific importance, but the methodology used is disputable and even today it remains insufficiently standardized. There are no conclusive data what percentage of missed treatment days make bisphosphonates treatment ineffective. Even by the most liberal criteria, adequate reception of the drug in 66% of days of the healing period is the lowest limit for achieving therapeutic success. Treatment remains effective if treatment interruption is under 33% of treatment days. In our studies we have considered medication persistence quite good if treatment has been discontinued for less than 60 days during the 24-month period of observation; this is the interruption of prescribed therapy in 8.2% of days. Adherence of patients to the treatment depends on the BMD score, previous fractures, age, annual income, concomitant diseases, marital status, number of previous hospitalizations and the number of medications patients take in. The professional conduct and competence of doctors are of crucial importance. The severity and clinical manifestations of osteoporosis are also undoubtedly important. In most of the cases of inadequate treatment the reasons are complex. Patients should be adequately informed about the efficacy and route of administration of recommended medications and duration of treatment.

To combat the poor adherence to anti-absorptive treatment it is necessary to improve the treatment strategy and the use of simpler methods of administration. Extending the period between the administration of drugs can improve compliance to some degree. Introducing new osteoporosis drugs into practice may be successful if the drugs have better compliance. Certainly poor adherence to treatment is a problem specific to the administered drug.

In the observed postmenopausal women with osteoporosis a relatively high degree of consistency and adherence to treatment (medical persistence) to bisphosphonate was found. At 12 months the rate of medical persistence is high - 86.80%, while at the 24 months the degree of medical persistence is significantly reduced and is 58.94%. Adherence to treatment as measured by medication possession ratio in postmenopausal women not ceasing their treatment for 24 months is very high - 0.9788.

CONCLUSIONS

Adherence and consistency of treatment with bisphosphonates in postmenopausal osteoporosis is a significant problem in daily practice for rheumatologists, endocrinologists and orthopedists. The medication possession ratio, the method we used, can be applied in cases undergoing prolonged medical treatment for other chronic diseases such as hypertension, diabetes and gout. The index assesses the behaviour of patients during their treatment. On the
basis of the MPR scores we obtained we can reasonably assume that the treatment with bisphosphonates has been administered regularly, as prescribed, with only minor deviations from the rules.

REFERENCES
ПОСТОЯНСТВО И ПОСЛЕДОВАТЕЛЬНОСТЬ У ЖЕНЩИН (ПОСТ МЕНОПАУЗА) С ОСТЕОПОРОЗОМ К ЛЕЧЕНИЮ БИФОСФОНАТАМИ (BI-PHOSPHONATE/S)

С. Кузманова, П. Солаков, М. Генева-Попова

РЕЗЮМЕ

ВВЕДЕНИЕ: Остеопороз представляет собой костное заболевание метаболизма, причиной которого является уменьшение минеральной плотности кости (bone mineral density-BMD). Остеопороз – одна из больших проблем здравоохранения общества, так как значительно повышает риск фрактур позвонков, бедра, кисти, как и других костей.

ЦЕЛЬ: Исследование ставит себе целью установить степень постоянства и последовательности у женщин с остеопорозом после менопаузы к систематическому и продолжительному лечению бифосфонатами.

ПАЦИЕНТЫ И МЕТОДЫ: Период наблюдения пациентов – 24 мес. Рандомизировано 341 больного. Диагноз поставлен на основании клинических и рентгенологических данных и на основании DXA T-score более низкий, чем -2.5 SD (DXA) аксиального скелета и левого тазобедренного сустава. Применены терапии препаратами Alendronate 70 мг раз в неделю или Ibandronate 50 мг раз в месяц per os.

РЕЗУЛЬТАТЫ: Постоянство больных к назначенной терапии (Patient medication persistence) в конце 12-ого мес. – 86.80%, а в конце 24-ого мес. – 58.94%. Динамично изменяющиеся стоимости индекса medication possession ratio (MPR) к лечению бифосфонатами на 6-ой, 12-ый, 18-ый и 24-ый мес. колеблются в границах от 0.93 до 1.00. Они показывают высокую степень последовательности и приобщенности (Patient medication persistence) у наблюдаемых женщин к лечению бифосфонатами, продолжившему в течение 24 мес. Регулярный приём назначенной медикаментозной терапии (Patient medication persistence) снижается значительно в конце 12-ого мес.

ЗАКЛЮЧЕНИЕ: Согласие (compliance) больных проводить антирезобтивную терапию зависит как от социально-экономических условий, так и от поведения лечащего врача. В очень редких случаях лечение прекращается из-за побочных медикаментозных проявлений или из-за отсутствия убежденности у пациентов, что у них остеопороз.