ABSTRACT

Charles University, Faculty of Pharmacy in Hradec Králové

Department of	Department of Social and Clinical Pharmacy
Candidate	Mgr. Tereza Toušková
Supervisor	PharmDr. Magda Vytřísalová, PhD.
Title of Doctoral Thesis	QUALITATIVE AND QUANTITATIVE ASPECTS OF ADHERENCE TO OSTEOPOROSIS TREATMENT

Následuje překlad abstraktu práce do anglického jazyka.

Introduction: Non-adherence in the field of osteoporosis (OP) is considerable and it is necessary to deal with it because adequate adherence to the therapy leads to a reduction in the risk of fractures, the number of hospitalizations, and the cost of health care. Monitoring of the adherence is therefore an essential and integral part of patient care. The problem in osteoporotic patients is that 30-50% don´t follow the recommendations for proper use of the drugs, which is f.e. for the treatment of oral bisphosphonates (p.o. BIS) essential. Despite the availability of effective pharmacotherapy, approximately half of patients with OP aren´t adherent to the treatment regimen and / or discontinue treatment during the first year of use. Many different methods are used for adherence measurement, making the results difficult to compare. There still isn't a "gold standard" in the measurement of adherence, which would be widely used, which would allow relevant data on patient adherence to treatment to be obtained. To obtain valid results and more comprehensive ideas about adherence / non-adherence of the patients, it is recommended to combine the individual methods appropriately. An integral part of osteoporosis management is not only the adherence of patients to treatment but also the adherence of healthcare professionals. The goal of this management is to achieve rational treatment in the patient and thus maximize the effect and minimize the risks of therapy. General practitioners are key participants in osteoporosis management.

Objectives: (1) Compare adherence to p.o. BIS used in weekly or monthly regime with emphasis on dosing instructions; (2) For persistent patients taking a fixed Ca / D combination to study adherence focusing on the character of non-adherence, compare three different methods of adherence measurement (electronic monitoring with the Medication Event Monitoring System (MEMS), tablet counting and self-report questionnaire), and study

adherence obtained with MEMS over time and examine whether and how adherence is affected by entry into the study and visits by a physician. (3) Evaluate General practicioners adherence to management of the disease, potential barriers, and to discuss differences observed in comparison with the baseline survey carried out in 2007

Methods: (1) A multicenter, prospective, cross-sectional study was carried out in an anonymous questionnaire survey. The study included 5 health care facilities in the Czech Republic, which specialized in the care of patients with OP. The study included women older than 55 years with diagnosed OP or osteopenia who were treated with p.o. BIS in a weekly or monthly regime. Adherence to the manufacturer's instruction was evaluated (Summary of Product Characteristics) to ensure the safety and adequate absorption of bisphosphonates with 5 questions on the use. Four adherence scores for dosing instructions were calculated: adherence to all five dosing instructions, adherence to dosing instructions ensuring adequate absorption, adherence to dosing instructions preventing adverse events, and adherence to dosing instructions concerning time interval. Patient's attitudes were also evaluated. These attitudes included the necessity for treatment and treatment concerns ("necessity / concern" concept) and were classified using the Beliefs on Medicines Questionnaire - Specific (BMQ-S). The BMQ-S contained 10 questions with 5 alternative responses from fully agree (5 points) to strongly disagree (1 point); (2) 73 patients were enrolled in the first round of the observational study, 49 patients who met the persistence condition were analyzed. They were treated with p.o. Ibandronate and Ca / D supplementation. The adherence was evaluated for 3 months using the Medication Event Monitoring System (MEMS), tablet counting and self-reported questionnaire. The first round of the study included 3 months in 2013, this year the patients underwent informed consent to enter the study, the second round followed after about 12 months and started with the usual visit of the patient to the osteologist, it took 3 months, too. After 12 months, adherence was compared. (3) We conducted a cross-sectional study among General Practitioners with data collection using a questionnaire. The questionnaire covered areas concerning General Practitioners role in the fight against OP, knowledge about OP, management of OP-related fractures, barriers to the management of OP, system- and patient-related in particular.

Results: (1) As many as 363 questionnaires were analyzed (mean age of 69 years). Respondents were treated with weekly bisphosphonates (37%) or monthly ibandronate (63%). 66 patients were treated with risedronate (18%) and 67 patients with alendronate (19%). Adherence to all five dosing instructions was reported by 44% participants. As many as 40%, 14% and 1% of participants were non-adherent to one, two or all five dosing instructions, respectively.

Adherence to the instructions depending on the time interval (staying upright long enough and fasting long enough), was 71% in the weekly and 52% in the monthly bisphosphonates (P <0.001). The mean score of the neccessity (18.4 points) was higher than the treatment concerns (13.3 points); (2) Based on the MEMS medication adherence in the first round was 71%. 71% of the patients took at least one drug holiday. Adherence of these patients was only 59%, and it was lower on Fridays and weekends. Adherence higher than 75% was observed in 59% (MEMS), 100% (tablet count), and 87% (self-report) patients. Adherence obtained after 12 months was 68% - there were no significant differences between it and the first round. In the comparision of individual months, the 1st month (in the first round) was significantly higher than in the second month, and at the same time, higher than in the 1st month in the 2nd round. The patterns of the adherence were similar in both rounds. More than 2/3 of the patients took drug holidays in both rounds. (3) The study enrolled 551 respondents (mean age 53, 37% male). The General practitioners role in the treatment of OP was rated as essential in 28% and 37% of men and women, respectively ($P = 0.012$). As much as 60% of the respondents were adherent to the guidelines, i.e., used it repeatedly. The knowledge of several risk factors was very good. However, recommended daily intake of calcium was stated correctly by only 41% of respondents, and daily intake of vitamin D by only 40%. Three quarters reported active steps after a fracture. Half of the respondents focused on fall prevention. System-related barriers, such as lack of possibility to prescribe selected drugs (61%) and financial limits set by health insurance companies (44%) were the most frequently reported. Patient-related barriers were also common, such as patient's non-adherence (reported by 29%) and patient's reluctance to go to a specialist (18%).

Discussion and conclusion: (1) Most patients do not follow dosing instructions; adherence to all recommendations for safe and adequate absorption of p.o. BIS was low. The primary problem is the required interval (1 hour) between the use of ibandronate and food / other drugs and the need to stay upright for the same time. Therefore, reduced bioavailability, particularly of monthly ibandronate, can be expected in clinical practice. With sufficient patient education and explanations of specific reasons for adhering to the recommendations (protection against side effects, adequate absorption of the drug), adherence may be increased. In addition, the benefit of education may be that patient concerns will be reduced, and a higher understanding of the necessity of treatment will be achieved which may increase overall adherence to treatment; (2) Good adherence (≥80%) to Ca / D supplementation therapy was observed in 60% of patients. The most important aspect of non-adherence was the presence of drug holidays. In common clinical practice, emphasis should be placed on supporting the daily intake of

supplementation in patients at risk of osteoporotic fracture. Both the tablet counting and the self-reported questionnaire overestimated the adherence and did not provide a real picture of adherence of the patients compared to the results obtained by electronic monitoring. Adherence was inadequate (approximately 70%) either at the beginning (1st round) and follow-up after 12 months (2nd round). In individual months, it did not change significantly. Signature of informed consent appears to be a bias more than a regular medical check-up, but this phenomenon needs to be further investigated. (3) Knowledge of risk factors and involvement in post-fracture care was relatively high. Prescribing conditions and non-adherence of the patients are still important issues. Among GPs, education should be focused on calcium and vitamin D intake, doses, sources, and supplements.