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**Abstract**

***Objective:*** The present study was designed to assess the effect of monthly ibandronate on health-related quality of life (HR-QoL) in patients with postmenopausal osteoporosis previously treated with weekly bisphosphonates. ***Methods:*** HR-QoL was assessed by Euroqol (EQ-5D) and Osteoporosis Targeted Quality of Life (OPTQoL) questionnaires. ***Results:*** The EQ-5D questionnaire showed significant improvement associated with ibandronate treatment occurring in mobility ($p<0.01$), usual activity ($p<0.01$), pain/discomfort ($p<0.05$) and anxiety/depression ($p<0.05$). In addition, ibandronate treatment considerably improved patients perceived health on a visual analogue scale ($p<0.001$). For the OPTQoL questionnaire patients reported less physical difficulty ($p<0.001$), fewer adaptations in their lives ($p<0.001$) and less fear ($p<0.001$), with ibandronate than with weekly bisphosphonates. ***Conclusion:*** the study demonstrated that patients who were transferred from weekly bisphosphonates to a monthly ibandronate experienced improved HR-QoL.

**Key Words:** bisphosphonates, osteoporosis, quality of life, EQ-5D, OPTQoL

## Introduction

Health-related quality of life (HR-QoL) represents an important endpoint in the evaluation of patients with chronic diseases. Osteoporosis is a systemic bone disease that affects various aspects of a patient's life. A number of studies showed impaired QoL in patients with postmenopausal osteoporosis (1-4). These patients may be plagued by fear of fracture and consequent loss of independence which may lead to changes in psychosocial behaviour such as depression. Furthermore, low trauma fracture, the major consequence of osteoporosis, could be associated with chronic pain which considerably impairs patient's QoL.

Over the last two decades bisphosphonates were considered the mainstay of treatment for postmenopausal osteoporosis. A substantial number of studies confirmed the effectiveness of various bisphosphonates on vertebral and proximal femur bone mineral density (BMD) gain, reduction of bone turnover markers and, finally, prevention of fracture (5-8). However, efficacy of treatment should not be evaluated only by BMD increase and fracture risk reduction but also by HR-QoL improvement. A majority of pivotal studies were inadequately designed to demonstrate the treatment effects on QoL. Nevertheless, some of them using different drugs available for the treatment of osteoporosis reported certain improvement in the patient's QoL (9-11).

One of the major problems with bisphosphonate use is poor adherence to therapy. This is probably related to complicated dosing instructions and poor gastrointestinal tolerability which certainly have an impact on QoL. Several studies reported improved adherence with reducing bisphosphonate dosing frequency (12, 13). Moreover, data has shown that less frequent dosing is more convenient for the patient (14-16).

Direct head-to-head studies investigating the effect of different bisphosphonates on fracture risk reduction are lacking. A few studies have compared their effect on bone markers

and BMD (17, 18). Conversely, similar studies of HR-QoL outcomes have not been performed. In view of this consideration, the present study was designed to assess the effect of monthly ibandronate on HR-QoL in patients with postmenopausal osteoporosis previously treated with weekly bisphosphonates. We hypothesized that these patients will experience certain improve of HR-QoL.

## Materials and methods

### *Study design*

This was a prospective, open-label, multi-centre study. Fourteen centres in Croatia were included. The study comprises two visits in a six month interval (visit window ±1 month). At the baseline, patients were switched from weekly bisphosphonates to monthly ibandronate. There was no wash-out period between the two treatment regimens. QoL questionnaires were completed at baseline and at the end of the study.

### *Patients*

The ITT populations comprised 395 patients with postmenopausal osteoporosis whereas 385 patients aged 66.6±8.1 years were available for the per-protocol analyses. Eligible were women who have been treated for osteoporosis with weekly alendronate or risedronate for at least six months prior to enrolment in the study. Excluded were patients receiving corticosteroids or any other drug that influences bone metabolism, had any disease that affects bone metabolism, had history of malignant disease or had any other disease that significantly impairs QoL such as significant upper gastrointestinal disease, active nephrolithiasis, severe osteoarthritis, rheumatoid arthritis, significant renal or liver disease, etc. Written informed consent was obtained by all participants. The study has been approved by The Local Ethics Committee.

### *QoL questionnaires*

HR-QoL was assessed by Euroqol (EQ-5D) and Osteoporosis Targeted Quality of Life (OPTQoL) questionnaires.

EQ-5D is a two-part questionnaire comprising five questions that cover five dimensions of health: mobility, self-care, pain/discomfort, usual activity and

anxiety/depression (for each dimension there are three possible answers indicating no problems, some problems or severe problems) and self-related global valuation of perceived health using a visual analogue scale graded 0 to 100 (0= worst possible health; 100= perfect health) (19).

The OPTQoL is a disease specific instrument designed to assess the impact of osteoporosis on a patient's QoL (20). It measures three different dimensions of health: physical difficulty, adjustments, and fears. The physical difficulty domain focuses on having difficulties performing certain activities. It contains 7 items that are rated on a 5-point Likert scale. The adjustments domain focuses on planning certain activities. It contains nine items which are rated on a 4-point Likert scale. The fears domain focuses on fears of sustaining pain or injuries while performing certain activities. It contains six items which are rated on a 4-point Likert scale. The scores for each domain were converted to a 0 to 100 scale where higher scores indicate better quality of life.

***Statistical analysis***

All statistical analyses were performed using STATISTICA (version 8.0). Data are presented as median, minimum, maximum and interquartile range and proportions. Normal distribution and homogeneity of the variances were tested using Lindman's and Shapiro-Wilk's W test. Differences between 2 points of measurements were analysed using ANOVA/ MANOVA for repeated measurements. Differences in the prevalence of individual conditions were measured using $chi^2$ test. The level of significance of correlation between variables and the correlation trend were analyzed by the Pearson Correlation Test. Statistical significance was defined as a p value of 0.05 ($p<0.05$) in all analyses.

**Results**

A total of 395 patients met the inclusion criteria and were enrolled in the study at 14 study centres in Croatia. Of these 395 patients**,** complete data was available for 385 (97.5%). The other 10 (2.5%) patients withdrew from the study: 5 (1.3%) patients did not start monthly ibandronate according to the suggestion of their attending doctor, 4 (1.0%) patients had gastrointestinal adverse events and 1 (0.2%) patient was lost to follow up (Figure 1). No significant differences in any of the EQ-5D and OPTQoL domains at baseline were noted between the patients who completed the study and those who withdrew.

The proportion of patients reporting any problems in each of the five domains of EQ-5D at both study visits are presented in Table 1. The greatest improvement associated with ibandronate treatment occurred on mobility ($p<0.01$) and usual activity ($p<0.01$), followed by pain/discomfort ($p<0.05$) and anxiety/depression ($p<0.05$). Conversely, for the item self-care, although ibandronate treatment prompted some improvement, the difference was not significant. In accordance with the above data, ibandronate treatment considerably improved patients perceived health on a visual analogue scale (median 70, IR 51-80 vs. median 70, IR 60-80; $p<0.001$).

Figure 2 provides three OPTQoL subscale scores at baseline and 6 months after administration of ibandronate. Patients reported less physical difficulty (median 0.68, IR 0.50-0.84 vs. median 0.61, IR 0.46-0.79; $p<0.001$), fewer adaptations in their lives (median 0.56, IR 0.50-0.64 vs. median 0.53, IR 0.44-0.64; $p<0.001$), and less fear (median 0.71, IR 0.50-0.88 vs. median 0.63, IR 0.42-0.83; $p<0.001$), with ibandronate than with weekly bisphosphonates.

**Discussion**

Many comparative studies investigating the effect of different bisphosphonates on bone markers and bone mineral density have been carried out. The present study offers additional information regarding the impact of weekly and monthly bisphosphonates on HR-QoL in patients with postmenopausal osteoporosis. Most recently, few studies demonstrated patient's preference for monthly ibandronate over weekly alendronate and risedronate (14-16, 21) which is likely to influence therapeutic adherence and subsequently could have an impact on treatment efficacy. However, these studies did not address the issue of HR-QoL which is an important attribute of patient care.

In our previous study exploring patient's preference for different dosing regimens of bisphosphonate administration (14) a majority of the patients reported better QoL with monthly ibandronate than weekly bisphosphonates. Still, the study was not adequately designed to detect differences in QoL.

Therefore, the main goal of the present study was to assess the effect of monthly ibandronate on HR-QoL in patients with postmenopausal osteoporosis previously treated with weekly bisphosphonates. For this purpose, two questionnaires, EQ-5D and OPTQoL, were used to analyse different dimensions of QoL. EQ-5D is a generic instrument whose main advantage is that its scores can be compared with other conditions. However, it does not precisely identify whether QoL changes are due to bisphosphonate treatment or some other condition. Therefore, the EQ-5D was combined with OPTQoL, a disease-targeted questionnaire that covers more specific aspects of osteoporosis. Our finding demonstrated that almost all aspects of HR-QoL measured by EQ-5D and OPTQoL were improved in the six months following a treatment with ibandronate compared with the baseline. We believe this is

the first report of better HR-QoL in patients with postmenopausal osteoporosis associated to one treatment over another.

The basis behind the improved HR-QoL in patients receiving monthly ibandronate after previous treatment with weekly bisphosphonates remains to be clarified. Vertebral and non-vertebral fractures are major factors that affect patient's QoL. The recent head-to-head database fracture study demonstrated significantly lower relative risk of vertebral fracture in patients receiving ibandronate than weekly bisphosphonates (22). However, the present study was not designed to asses the number and location of vertebral fractures either at baseline or at the end of the study. The relative risk reduction of vertebral fractures, at least in part, could be related to therapeutic adherence which has shown improvement with the reduced dosing frequency. Several studies reported superior patient's adherence to monthly compared with weekly bisphosphonates (12, 13).

Another important issue is a chronic back pain related to vertebral fractures which is frequently one of the first symptoms of established osteoporosis. In the recent review on ibandronate and other bisphosphonates, the authors conclude that ibandronate offers an effective and convenient choice for the relief of bone pain in a variety of underlying bone diseases (23). Although this has been well proven in malignant conditions, similar data in osteoporosis is limited.

Complicated bisphosphonate dosing instructions, specific time restrictions and gastrointestinal tolerability are important issues which could be related to compromised QoL in patients with postmenopausal osteoporosis. There is a strong evidence that monthly ibandronate is preferred by patients over weekly bisphosphonates (14-16, 21). Similarly, a majority of patients stated that a monthly dosing regimen is more convenient and better fitted to their lifestyle. Moreover, several studies reported significantly lower incidence of adverse events associated with monthly compared to weekly bisphosphonates (14, 24).

Though osteoporosis has a considerable effect on a variety of physical aspects of a patient's life, the emotional dimensions of the disease, such as fear of falling and fear of changes in physical appearance, should not be underestimated. These patients are often anxious and worried which could result in depression (25). In the present study, significant difference in favour of ibandronate was observed in the anxiety/depression domain of EQ-5D and fear domain of OPTQoL.

Potential limitations of the study involved lack of cross-over design as there was no control study group previously on monthly ibandronate switching to weekly bisphosphonates. Moreover, the study had an open-label design. However, this was inevitable as the study was set to reflect the situation we have in every day clinical practice. Another limitation of the study relates to the relatively short follow-up time (6 months).

To summarize, the present study demonstrated that patients who were transferred from weekly bisphosphonates to a monthly ibandronate experienced improved HR-QoL. We suggest this issue to be taken into account when considering treatment options. New studies using cross-over design are needed to further support our results.

**Declaration of interest**

The authors report no conflicts of interest.

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