



Središnja medicinska knjižnica

Kaštelan D., Vlak T., Lozo P., Gradišer M., Mijić Š., Nikolić T., Miškić B., Car D., Tajsić G., Dušek T., Jajić Z., Grubišić F., Poljičanin T., Bakula M., Džubur F., Strižak-Ujević M., Kadojić M., Radman M., Vugrinec M., Kušter Ž., Pekez M., Radović E., Labar Lj., Crnčević-Orlić Ž., Koršić M. (2010) *Health-related quality of life among patients with postmenopausal osteoporosis treated with weekly and monthly bisphosphonates*. *Endocrine Research*, 35 (4). pp. 165-73. ISSN 0743-5800

<http://informahealthcare.com/journal/erc>

<http://dx.doi.org/10.3109/07435800.2010.505218>

<http://medlib.mef.hr/1426>

University of Zagreb Medical School Repository

<http://medlib.mef.hr/>

Title: Health-related quality of life among patients with postmenopausal osteoporosis treated with weekly and monthly bisphosphonates

Running Head: QoL among patients treated with bisphosphonates

Authors: Darko Kastelan, prof., M.D., Ph.D.¹, Tonko Vlak, prof., M.D., Ph.D.², Petar Lozo, M.D.³, Marina Gradiser, M.D.⁴, Sime Mijic, M.D.⁵, Tatjana Nikolic, M.D.⁶, Blazenka Miskic, M.D.⁷, Dolores Car, M.D.⁶, Gordana Tajsic, M.D.⁶, Tina Dusek, M.D.¹, Zrinka Jajic, prof.,M.D.,Ph.D.⁸, Frane Grubisic, M.D.⁸, Tamara Poljicanin, M.D.⁹, Miro Bakula,M.D.¹⁰, Fedja Dzibur,M.D.¹, Matilda Strizak-Ujevic, M.D.¹¹, Mira Kadojic,M.D.¹², Maja Radman, M.D.¹³, Maja Vugrinec¹⁴, Zeljka Kuster¹⁴, Marijeta Pekez¹⁴, Endi Radovic, M.D.¹⁵, Ljubica Labar, M.D.¹⁶, Zeljka Crncevic-Orlic, prof., M.D., Ph.D.¹⁷, Mirko Korsic, prof., M.D., Ph.D.¹

Affiliations of the authors:

Department of Endocrinology, University Hospital Zagreb, Zagreb, Croatia¹

Department of Rehabilitation Medicine and Rheumatology, University Hospital Split, Split, Croatia²

Outpatient clinic for Gynaecology Lozo, Zadar, Croatia³

Department of Internal Medicine, County Hospital Cakovec, Cakovec, Croatia⁴

Health Medical Centre for Physical Medicine and Rehabilitation, Jastrebarsko, Croatia⁵

University Clinic of Traumatology, Zagreb, Croatia⁶

Department of Internal Medicine, General Hospital Dr. Josip Bencevic, Slavonski Brod, Croatia⁷

Department of Rheumatology, Physical Medicine and Rehabilitation, University Hospital
"Sestre Milosrdnice", Zagreb, Croatia⁸

Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Zagreb,
Croatia⁹

Department of endocrinology, diabetes and metabolic disorders, General Hospital "Sv. Duh",
Zagreb, Croatia¹⁰

General Hospital Sibenik, Sibenik, Croatia¹¹

Department of Physical Medicine and Rehabilitation, University Hospital Osijek, Osijek,
Croatia¹²

Department of Endocrinology, Diabetes and Metabolism, University Hospital Split, Split,
Croatia¹³

School of Medicine University of Zagreb, Zagreb, Croatia¹⁴

Department of Physical and Rehabilitation Medicine, University Hospital Rijeka, Rijeka,
Croatia¹⁵

Special Hospital for Orthopaedics, Biograd, Croatia¹⁶

Department of Endocrinology, University Hospital Rijeka, Rijeka, Croatia¹⁷

Corresponding author:

Darko Kastelan, M.D., Ph.D.

Division of Endocrinology, Department of Internal Medicine, University Hospital Zagreb

Kispaticeva 12, 10000 Zagreb, Croatia

Tel/fax + 385-1-2421-867

e-mail: dkastelan@inet.hr

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 chi² 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 assess 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.

References:

1. Silverman, S.L., Minshall, M.E., Shen, W., Harper, K.D., Xie, S.; Health-Related Quality of Life Subgroup of the Multiple Outcomes of Raloxifene Evaluation Study. (2001). The relationship of health-related quality of life to prevalent and incident vertebral fractures in postmenopausal women with osteoporosis: results from the Multiple Outcomes of Raloxifene Evaluation Study. *Arthritis Rheum* 44;2611-2619.
2. Cook, D.J., Guyatt, G.H., Adachi, J.D., et al. (1993). Quality of life issues in women with vertebral fractures due to osteoporosis. *Arthritis Rheum* 36;750-756.
3. de Oliveira Ferreira, N., Arthuso, M., da Silva, R., Pedro, A.O., Neto, A.M., Costa-Paiva, L. (2009). Quality of life in women with postmenopausal osteoporosis: correlation between QUALEFFO 41 and SF-36. *Maturitas* 62;85-90.
4. Romagnoli, E., Carnevale, V., Nofroni, I., et al. (2004). Quality of life in ambulatory postmenopausal women: the impact of reduced bone mineral density and subclinical vertebral fractures. *Osteoporos Int* 15;975-980.
5. Liberman, U.A., Weiss, S.R., Bröll, J., et al. (1995). Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med* 333;1437-1443.
6. Reginster, J., Minne, H.W., Sorensen, O.H., et al. (2000). Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos Int* 11;83-91.
7. Harris, S.T., Watts, N.B., Genant, H.K., et al. (1999). Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized, controlled trial. *JAMA* 282;1344-1352.

8. Chesnut III, C.H., Skag, A., Christiansen, C., et al.; Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE). (2004). Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res* 19;1241-1249.
9. Yoh, K., Tanaka, K., Ishikawa, A., et al. (2005). Health-related quality of life (HRQOL) in Japanese osteoporotic patients and its improvement by elcatonin treatment. *J Bone Miner Metab* 23;167-173.
10. Maugeri, D., Russo, E., Luca, S., et al. (2009). Changes of the quality-of-life under the treatment of severe senile osteoporosis with teriparatide. *Arch Gerontol Geriatr* 49;35-38.
11. Marquis, P., Roux, C., de la Loge, C., et al. (2008). Strontium ranelate prevents quality of life impairment in post-menopausal women with established vertebral osteoporosis. *Osteoporos Int* 19;503-510.
12. Cotté, F.E., Fardellone, P., Mercier, F., Gaudin, A.F., Roux, C. (2010). Adherence to monthly and weekly oral bisphosphonates in women with osteoporosis. *Osteoporos Int* 21;145-155.
13. Lewiecki, E.M., Babbitt, A.M., Piziak, V.K., Ozturk, Z.E., Bone, H.G. (2008). Adherence to and gastrointestinal tolerability of monthly oral or quarterly intravenous ibandronate therapy in women with previous intolerance to oral bisphosphonates: a 12-month, open-label, prospective evaluation. *Clin Ther* 30;605-621.
14. Kastelan, D., Lozo, P., Stamenkovic, D., et al. (2009). Preference for weekly and monthly bisphosphonates among patients with postmenopausal osteoporosis: results from the Croatian PROMO Study. *Clin Rheumatol* 28;321-326.
15. Emkey, R., Koltun, W., Beusterien, K., et al. (2005). Patient preference for once monthly ibandronate versus once-weekly alendronate in a randomized, open-label,

- cross-over trial: The Bonviva Alendronate Trial in Osteoporosis (BALTO). *Curr Med Res Opin* 21;1895-1903.
16. Hadji, P., Minne, H., Pfeifer, M., et al. (2008). Treatment preference for monthly oral ibandronate and weekly oral alendronate in women with postmenopausal osteoporosis: A randomized, crossover study (BALTO II). *Joint Bone Spine* 75;303-310.
 17. Sebba, A.I., Bonnick, S.L., Kagan, R., et al. Fosamax Actonel Comparison Trial investigators. (2004). Response to therapy with once-weekly alendronate 70 mg compared to once-weekly risedronate 35 mg in the treatment of postmenopausal osteoporosis. *Curr Med Res Opin* 20;2031-2041.
 18. Emkey, R., Delmas, P.D., Bolognese, M., et al. (2009). Efficacy and tolerability of once-monthly oral ibandronate (150 mg) and once-weekly oral alendronate (70 mg): additional results from the Monthly Oral Therapy With Ibandronate For Osteoporosis Intervention (MOTION) study. *Clin Ther* 31;751-761.
 19. Rabin, R. (2001). EQ-5D: a measure of health status from the EuroQoL group. *Ann Med* 33;337-343.
 20. Lydick, E., Zimmerman, S.I., Yawn, B., et al. (1997). Development and validation of a discriminative qualitative of life questionnaire for osteoporosis (the OPTQoL). *J Bone Mineral Res* 12;456-463.
 21. Bonnick, S.L., Silverman, S., Tanner, S.B., et al. (2009). Patient satisfaction in postmenopausal women treated with a weekly bisphosphonate transitioned to once-monthly ibandronate. *J Womens Health (Larchmt)*, Doi:10.1089/jwh.2008.1064.
 22. Harris, S.T., Reginster, J.Y., Harley, C., et al. (2009). Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: the eValuation of Ibandronate Efficacy (VIBE) database fracture study. *Bone* 44;758-765.

23. Ringe, J.D., Body, J.J. (2007). A review of bone pain relief with ibandronate and other bisphosphonates in disorders of increased bone turnover. *Clin Exp Rheumatol* 25;766-774.
24. Derman, R., Kohles, J.D., Babbitt, A. (2009). Gastrointestinal tolerability with ibandronate after previous weekly bisphosphonate treatment. *Clin Interv Aging* 4;357-365.
25. Martin, A.R., Sornay-Rendu, E., Chandler, J.M., Duboeuf, F., Girman, C.J., Delmas, P.D. (2002). The impact of osteoporosis on quality-of-life: the Ofely Cohort. *Bone* 31; 32-36.