

# Prospective Clinical Study of Once Monthly Ibandronate in the Treatment of Osteoporosis and Prevention of Fractures in Postmenopausal Women: ORPHEUM Study

Marko Bumbaširević<sup>1,2</sup>, Aleksandar Lešić<sup>1,2</sup>, Ljiljana Denić-Marković<sup>3</sup>, Kristina Živković<sup>1,2</sup>; and ORPHEUM Study Group

<sup>1</sup>Clinic for Orthopaedic Surgery and Traumatology, Clinical Centre of Serbia, Belgrade, Serbia;

<sup>2</sup>School of Medicine, University of Belgrade, Belgrade, Serbia;

<sup>3</sup>Institute for Epidemiology, School of Medicine, University of Belgrade, Belgrade, Serbia

## SUMMARY

**Introduction** Osteoporosis is a serious problem, since about 50% of women over the age of 50 suffer at least one osteoporotic fracture.

**Objective** The aim of this study was to evaluate compliance as well as the efficiency and safety of ibandronate treatment over a 6-month period in reducing the risk of subsequent fracture in women with postmenopausal osteoporosis.

**Methods** A multicenter, prospective, observational study was conducted during one year in thirteen medical centres in Serbia. In the first part of the study the participants received ibandronate tablets (150 mg) once a month for six months. In the second part, the patients were under clinical follow-up.

**Results** The mean age of the 184 menopausal women included in the study was 66.2±9.4 years. In 40.2% of the subjects the disease had been clinically manifest during the five preceding years. The mean T-score value at the onset of our investigation was -3.1±0.84 in 160 (87%) patients who were diagnosed osteoporosis. Compression vertebral fractures alone were noted in 24% of the women, spontaneous nonvertebral fractures in 49.4% and both in 4.9%. A history of osteoporotic fractures was much more common in patients with three or four risk factors ( $p=0.001$ ). Out of 39 adverse events during therapy with once monthly bisphosphonates only 2 (3.3%) were classified as severe. During the treatment, spontaneous fractures occurred in 13 (7.1%) patients.

**Conclusion** Ibandronate treatment once a month for 6 months was shown to be very safe, tolerated well and without more serious side effects.

**Keywords:** osteoporosis; bisphosphonates; fracture; prevention; treatment

## INTRODUCTION

Osteoporosis is defined as a systemic disorder with reduced body mass and microarchitectural defects of the bone tissue. It is a serious problem, since about 50% of women over the age of 50 suffer at least one osteoporotic fracture [1]. Increased fragility as well as reduced bone resistance predispose to the increased risk of fractures. The possibility of measuring bone mineral density (BMD) enables patients at increased risk to be identified even before the occurrence of fracture, thus treatment can be initiated on time [2]. Dual energy X-ray absorptiometry (DXA) for the assessment of bone mineralization is the gold standard for establishing the diagnosis of osteoporosis. A multidisciplinary approach is the key in both diagnosis and treatment of this condition. Non-pharmacological treatment methods, including food supplements (vitamin D and calcium) and a change in lifestyle, complement the pharmacological treatment of osteoporosis and mitigation of risk factors. Among the number of medicaments available for therapy, bisphosphonates are recognized as highly important.

Bisphosphonates are an antiresorptive class of drugs efficient in both prevention and treatment of osteoporosis [3]. They interfere in the normal resorptive metabolic pathway of osteoclasts [4]. Randomized clinical studies have shown that oral administration of bisphosphonates increases bone mineral density, thus decreasing the risk of fractures in women with postmenopausal osteoporosis [5, 6]. A daily dose schedule of oral bisphosphonates has been shown to lessen the risk of both vertebral and non-vertebral fractures. However, newer dosing schedules (once a week, once a month and once in three months) have also been beneficial and they are simpler to use than daily administration [5-8].

Oral ibandronate was the first oral bisphosphonate that can be used once a month for treating osteoporosis in postmenopausal women [9]. Applied in the dose of 150 mg once a month it is equally efficient at increasing BMD and reducing bone remodeling markers in older women with osteoporosis in whom tolerance appears to be better than with once a day administration [9].

## Correspondence to:

Aleksandar LEŠIĆ  
Clinic for Orthopaedic Surgery  
and Traumatology  
Clinical Centre of Serbia  
Dr Koste Todorovića 26  
11000 Belgrade  
Serbia  
alesic@sbb.rs

## OBJECTIVE

The purpose of this study was to evaluate the efficiency, safety and compliance with ibandronate treatment over a 6-month period in reducing the risk of subsequent fracture in women with postmenopausal osteoporosis.

## METHODS

Our multicenter, prospective, observational study was conducted from June 2008 to June 2009. Thirteen centres participated. The subjects were women only. The inclusion criteria comprised reduced BMD index (osteoporosis or osteopenia), age (older than 45 years), menopause and risk factors for fractures. All patients gave their informed consent for participation in the study. Each subject filled in a questionnaire including data on demographic features, reproductive status, physical activities and main risk factors for osteoporosis (fractures in adulthood, low body mass, smoking, alcohol consumption, use of oral corticosteroids for three or more months and rheumatoid arthritis). Physical activity was defined as low if the subject walked less than 1 hour out of home daily; moderate – more than 1 hour and significant if the subject exercised at least three times a week. Other accompanying diseases were also taken into account. A part of the questionnaire covered the mode of establishing the diagnosis; DXA, and or skeletal X-ray, profile of the specialist making the diagnosis (orthopaedic surgeon, endocrinologist, physiatrist or primary care physician). The questionnaire also included information on previous treatment of osteoporosis and BMD values, as well as T-score, specific for the location where they were obtained, up to 3 months before the ibandronate treatment was started.

In the first part of the study the subjects received ibandronate 150 mg tablets once a month for 6 months. After 6 months of ibandronate treatment, the patients underwent clinical follow-up examination in order to detect any spontaneous fractures and the occurrence of adverse effects of the drug. Follow-up DXA was not performed.

Descriptive statistics (means, standard deviation, proportions) was used to analyse the data, while the chi-square test was used to identify significance of differences among some of the variables.

## RESULTS

### Population description

The study comprised 184 women who were treated in healthcare institutions in Serbia due to a history of fractures caused by little or no force or osteoporosis. The youngest patient was 46 and the oldest 89 years old (mean age  $66.2 \pm 9.4$  years). All women were postmenopausal and only six (3.3%) received hormone substitution therapy. The average duration from the last menses was  $18.5 \pm 9.2$  years.

Education-wise, the largest number (44.0%) had a secondary school diploma, followed by 21.7% with a

**Table 1.** Type of fracture in patients with osteoporosis and osteopenia

Type of fracture	Number of patients		
	Osteoporosis	Osteopenia	Total
Compressive vertebral fractures only	44 (27.5%)	0 (0.0%)	44 (23.9%)
Spontaneous nonvertebral fracture only	75 (46.9%)	16 (66.7%)	91 (49.4%)
Associated compressive vertebral fractures and spontaneous nonvertebral fracture	9 (5.6%)	0 (0.0%)	9 (4.9%)
No fractures	32 (20.0%)	8 (33.3%)	40 (21.7%)
Total	160 (87.0%)	24 (13.0%)	184 (100.0%)

college/university degree and 27.7% with elementary education, while 6.5% had no education whatsoever.

### Diagnosis of the disease

In 74 (40.2%) subjects the disease was clinically manifested over five preceding years. No DXA or X-ray was made in 29 (15.8%) women before our study. A DXA scan was made in 85 (46.2%) subjects (40% DXA of the spine, 28% hip but for 32% data on the site were not specified).

In addition to DXA, 32 patients were X-rayed. As 85 more patients were X-rayed this technique was used for diagnosis in a total of 117 (63.3%) patients.

The mean T-score value at the beginning of the study was  $-3.1 \pm 0.84$  in 160 (87%) patients substantiating the diagnosis of osteoporosis, while osteopenia was diagnosed in 24 (13%) patients. In 92.1% cases the diagnosis was established by an orthopaedic surgeon. Table 1 shows the history of compressive fractures and spontaneous non-vertebral fractures in our subjects. All compression vertebral fractures and all histories of incident fractures were recorded in patients with osteoporosis. Out of 100 patients with a spontaneous non-vertebral fracture, 38% had a hip fracture, 34% a lower arm-wrist fracture, 10% an upper arm fracture and 18% had a fracture at some other location.

### Risk factors for osteoporosis

Almost all our patients (96.2%) had some of the main risk factors for the development of osteoporosis. On average, each had nearly two factors ( $1.6 \pm 0.8$ ). Only three patients (1.6%) had the maximum number of four risk factors. A history of osteoporotic fractures was much more common in patients with three or four risk factors ( $\chi^2=18.5$ ;  $df=4$ ;  $p=0.001$ ) (Table 2).

Association of the history of fractures with the presence of risk factors is presented in Table 3. Fractures were more common ( $p=0.001$ ) in women with a family history of fractures, as well as in women receiving oral corticosteroid treatment for over 3 months ( $p=0.02$ ). The level of exercise was low in 74 (40.2%) subjects. Only a very low percentage (8.2%) of patients exercised actively or pursued any physi-

**Table 2.** Number of pretreatment fractures in relation to the number of risk factors

Risk factors for osteoporosis	Pretreatment fractures		Total
	No	Yes	
0	3 (2.2%)	4 (8.2%)	7 (3.8%)
1	72 (53.3%)	11 (22.4%)	83 (45.1%)
2	44 (32.6%)	20 (40.8%)	64 (34.8%)
3	15 (11.1%)	12 (24.5%)	27 (14.7%)
4	1 (0.7%)	2 (4.1%)	3 (1.6%)
Total	135 (73.4%)	49 (26.6%)	184 (100.0%)

**Table 3.** Risk factors in patients with osteoporosis

Risk factor	Number of patients with history of fractures	Number of fractures	P
Low level of physical activity	51 (37.8%)	23 (46.9%)	0.26
Fractures in adulthood	52 (39.3%)	33 (67.3%)	0.001
Low body mass (<58 kg)	34 (25.2%)	14 (28.6%)	0.70
Smoking	40 (29.6%)	20 (40.8%)	0.16
Alcohol	5 (3.7%)	3 (6.1%)	0.44
Use of oral corticosteroids >3 months	10 (7.4%)	10 (20.4%)	0.03
Rheumatoid arthritis	7 (5.2%)	6 (12.2%)	0.11
Family history of fractures in the elderly	60 (44.4%)	9 (18.4%)	0.001

cal activity at least three times a week. There was no significant difference in the occurrence of fractures in patients with a low level of physical activity and those that actively exercised. Moreover, no significant difference was noted when they were compared in terms of smoking status, alcohol consumption, low body mass or presence of rheumatoid arthritis.

### Previous treatment of osteoporosis

Before joining the study, 48 (26.1%) women received calcium for the treatment of osteoporosis, 36 (19.6%) vitamin D, 10 (5.4%) daily bisphosphonates, six (3.3%) weekly bisphosphonates, and 10 (5.4%) intravenous bisphosphonates.

### Bisphosphonate monthly treatment and its effects

Most of the patients (95.8%) received monthly bisphosphonates over a 6-month period. Forty-two experienced 61 adverse events during the study. In 39 cases (63.9%) association of the event and the administered drug could be established. Among these only two (3.3%) adverse events were classified as serious. The association and the severity of adverse events in patients receiving bisphosphonate monthly with the treatment are presented in Table 4. Nausea was the most common symptom reported in 18 (9.8%) patients, followed by vomiting in 6 (3.3%) and diarrhoea in four (2.2%) subjects.

During the treatment period, spontaneous fractures occurred in 13 (7.1%) patients. Most commonly it was a hip fracture (38.5%) or a vertebral fracture (30.8%). In most

**Table 4.** Adverse events in our patients on once a month oral treatment in relation to the duration of treatment

Duration of treatment (months)	Number of patients		
	Adverse events	Association of adverse events with study drug	Severe adverse event
1	17 (9.2%)	12 (70.6%)	-
2	11 (6.0%)	7 (63.6%)	1 (9.1%)
3	9 (4.9%)	6 (66.7%)	-
4	10 (5.4%)	4 (40.0%)	-
5	8 (4.3%)	4 (50.0%)	1 (12.5%)
6	6 (3.3%)	6 (100.0%)	-

cases the patients stated that they felt well after the treatment (22.3%) or better (20.2%), that the pain was relieved (7.6%) and that their mobility was improved (5.4%). Only 10.9% recorded no change and 7.6% complained of persistent pain. Out of 159 subjects asked whether they wished to continue the treatment 91.2% answered affirmatively.

### DISCUSSION

The ORPHEUM study was conducted in order to investigate the efficacy, adverse effects and compliance of ibandronate treatment in women with reduced BMD index in everyday clinical practice. All women included in the study were postmenopausal, of average age over 65 years. The majority of them had secondary or university education (65.7%).

At the beginning of the study most patients had osteoporosis diagnosed by an orthopaedic surgeon, which may suggest insufficient involvement of doctors in primary health care. In the light of serious and severe consequences of this chronic disease, such as hip and vertebral fractures associated with increased mortality, it is of utmost importance for osteoporosis to be diagnosed promptly and treatment initiated by a primary care physician (GP or a family doctor) [10]. In over 80% of the patients DXA of the spine or hip, or X-ray examination substantiated the diagnosis, where it had been established on time and precisely. As many as 23.9% patients had a history of compressive vertebral fracture and osteoporosis was diagnosed in all. Most of the previous spontaneous nonvertebral fractures were hip fractures. In a four-year follow-up study of 6,500 women over 55 years of age, Cauley et al. [11] showed that the relative risk of a fatal outcome after such a fracture was 2.15. The highest mortality was recorded in women with hip and vertebral fractures. It has been estimated that women aged 50 years or more have a 16% risk of having a hip fracture during their lifetime, 15% suffer a distal radial fracture and 32% a vertebral fracture [12]. Therefore, effective prevention of fractures in women with osteoporosis may reduce morbidity and mortality.

In addition to the menopause, the most important risk factors for osteoporosis include the occurrence of fractures in adulthood (46.7%) and a low level of exercise/physical activity (40.2%). A history of osteoporotic fractures was much more common in patients with three or four risk factors, those with a family history of fractures and those

using corticosteroids for over 3 months. Contrary to recent findings of Vujasinović-Stupar et al. [13] and Perez et al. [14], who reported a significant number of patients without risk factors for osteoporosis (29.5%), in our study almost all women had at least one of the eight major risk factors. This can be explained by the lower number of subjects in our investigation and their postmenopausal age as an eligibility criterion for enrolment. In this study smoking, alcohol consumption, low body weight and rheumatoid arthritis did not contribute to a higher incidence of history of osteoporotic fractures.

Before enrolment, the majority of our patients received dietary vitamin D and calcium supplements, while only 14.1% patients received bisphosphonates daily, weekly or intravenously.

Most of our patients (95.8%) received bisphosphonate treatment for all six months of the study, as planned in the design, indicating very satisfactory compliance. Compliance was greater than during the weekly bisphosphonate administration regime, suggesting improvement with a less frequent dosage schedule [15]. During the treatment the occurrence of serious adverse events was very rare (3.3%) and in no case was discontinuation of treatment required. In another study that lasted a year, the percentage of our patients with adverse events was higher (10.5%) [13]. The most common of these involved the gastrointestinal tract, including nausea, vomiting and diarrhoea, but they were tolerated well. Favourable tolerance of the monthly dosing schedule can be explained by its lower potential to induce irritation of the oesophageal mucosa [15]. A falling trend was noted in the incidence of adverse events as the study progressed; from 9.2% in the first month of drug administration to 3.3% in the sixth month. The percentage of adverse events was expected to fall further with continuation of the treatment.

Only 7% of our patients suffered a spontaneous fracture during the 6-month treatment. The fracture incidence in a recently conducted study (VIBE) was under 2% over a 12-month period [5]. It should be pointed out that women

over the age of 65 accounted for a substantial share of our sample, and they all had a large number of associated risk factors for fractures.

Over 80% of our patients confirmed loss of pain, improved mobility and an overall sense of improvement after the treatment. Probably because of such improvement, over 90% of our subjects stated that they would continue the treatment.

## CONCLUSION

Ibandronate treatment once a month for 6 months was safe, tolerated well and without serious adverse events that would require discontinuation. Also, the risk of subsequent fractures in the treated postmenopausal women was relatively low.

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## Проспективно клиничко испитивање примене једномесечне дозе ибандроната у лечењу остеопорозе и превенцији прелома код жена у постменопаузи – студија *ORPHEUM*

Марко Бумбаширевић<sup>1,2</sup>, Александар Лешић<sup>1,2</sup>, Љиљана Денић-Марковић<sup>3</sup>, Кристина Живковић<sup>1,2</sup>; *ORPHEUM* студијска група

<sup>1</sup>Клиника за ортопедску хирургију и трауматологију, Клинички центар Србије, Београд, Србија;

<sup>2</sup>Медицински факултет, Универзитет у Београду, Београд, Србија;

<sup>3</sup>Институт за епидемиологију, Медицински факултет, Универзитет у Београду, Београд, Србија

### КРАТАК САДРЖАЈ

**Увод** Остеопороза је озбиљан проблем, јер око 50% жена старијих од 50 година има најмање један остеопоротични прелом.

**Циљ рада** Циљ рада био је да се процене ефикасност, сигурност и комплијанса лечења ибандронатом током шест месеци, те утврди смањење ризика настанка консекутивних прелома код жена у постменопаузи.

**Методе рада** Мултицентрична, проспективна, опсервациона студија изведена је током једне године у 13 медицинских центара у Србији. У првој фази студије испитанице су примале 150 mg ибандроната (таблете) једном месечно током шест месеци. У другој фази вршено је клиничко праћење ефеката лечења.

**Резултати** Студија је обухватила 184 жене просечне старости 66,2±9,4 године. Код 40,2% испитаница обољење се кли-

нички испољило у претходних пет година. Просечна вредност *t*-скора била је -3,1±0,84 код 160 испитаница код којих је постављена дијагноза остеопорозе (87%). Прелом пршљенског тела уочен је код 24% испитаница, спонтани невертебрални преломи дијагностиковани су код 49,4% жена, док су оба типа прелома утврђена код 4,9% испитаница. Остеопоротични преломи били су много чешћи код жена са три или четири фактора ризика ( $p=0,001$ ). Од 39 нежељених дејстава која су се јавила током лечења бифосфоната, само два (3,3%) означена су као тешка нежељена дејства. Током лечења спонтани преломи су се јавили код 13 испитаница (7,1%). **Закључак** Лечење једномесечном дозом ибандроната током шест месеци показало се веома сигурним и без тежих нежељених дејстава лека, а болеснице су га добро подносиле. **Кључне речи:** остеопороза; бифосфонати; преломи; превенција; лечење

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