Srp Arh Celok Lek. 2010 Jan-Feb;138(1-2):56-61
ОРИГИНАЛНИ РАД / ORIGINAL ARTICLE
DOI: 10.2298/SARH1002056V
UDC: 616.71-007.233-02-085

Efficacy and Safety of Once Monthly Ibandronate Treatment in Patients with Reduced Bone Mineral Density – ESTHER Study

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SUMMARY

Introduction Osteoporosis usually affects post-menopausal women. Treatment is individualized and requires an approach that will provide long-term compliance to prevent fractures. Studies conducted so far suggest inadequate compliance and persistence in weekly bisphosphonate treatment (under 43% after a year of treatment). Ibandronate, as a powerful bisphosphonate, has made it possible for the first time to treat osteoporosis with a single tablet per month.

Objective Study of efficacy, safety and tolerance of ibandronate applied once a month in female patients with decreased bone mineral density (BMD).

Methods The prospective study was conducted in 34 centres in Serbia covering the total of 370 women with reduced BMD with ibandronate once a month. Demographic data, risk factors for osteoporosis, mode of diagnosis establishment, previous treatment for osteoporosis and concomitant diseases were investigated. Efficacy of the treatment was evaluated by T-score value after 12 months versus the baseline values. Tolerance of the treatment, compliance and adverse effects were recorded.

Results The sample included 97.5% post-menopausal women, 92.7% with osteoporosis. In 80% of the cases, the diagnosis was established by DXA measurement. In more than 90% of the sample, the level of physical activity was unsatisfactory, and 70% had an accompanying risk factor for osteoporosis in addition to menopause. After 12 months of treatment, 100% compliance was recorded in 84% of the patients and significant reduction ($p<0.0001$) of the bone mineral loss, regardless of the previous aminobisphosphonate treatment. The treatment was tolerated well, with no serious adverse reactions. Some, mainly gastrointestinal complaints, registered in the first month (6%), were significantly relieved ($p<0.0001$) after 12 months of treatment (1%).

Conclusion Ibandronate manifested significant improvement of the BMD after 12 months of treatment of patients with decreased BMD, with good tolerance and excellent treatment compliance.

Keywords: osteoporosis; bone mineral density; risk factors; bisphosphonates; ibandronate

INTRODUCTION

Data on osteoporosis as a common disease frequently associated with risk of fractures, particularly in the population of elderly women, are widely available [1, 2]. Fractures due to osteoporosis are a huge health problem because of high incidence, suffering they cause and associated cost. Hip fractures cause a high level of disability among these patients [3]. The greatest challenge in cases of osteoporosis is to find an adequate treatment of patients at high risk of fracture [2, 4, 5]. Treatment of osteoporosis requires the selection of the optimal treatment that will provide long-term compliance with the prescribed medication to improve bone mineral density (BMD) and bone strength, in order to reduce the risk of fracture [6, 7, 8]. There are many drugs that are effective in reduction of the risk of fracture, but it is not quite clear how to use them best for treatment. The discrepancy between routine treatment of patients with osteoporosis and those reported in large clinical trials where majority of patients have satisfactory reduction of the risk of fracture is quite notorious. It is quite probable that not all patients in clinical practice benefit from the treatment, whether due to the lack of compliance with the prescribed treatment or other concomitant diseases [6]. Low level of compliance and early discontinuation of treatment are important problems in treatment of osteoporosis.

Treatment of osteoporosis is monitored by the measurement of BMD in 1-2 year intervals and monitoring of bone resorption markers (N or C-telopeptide fragments of collagen type 1). In the course of anti-resorption treatment, the rise of lumbar BMD by >3-6%, and reduction of markers by >30-50% probably result in the treatment success, i.e. good response to the applied antiresorptive treatment [6].

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Ever since they were initially reported 30 years ago, bisphosphonates take a distinguished place in treatment of metabolic bone disease with increased osteolysis, such as Paget's diseases, bone metastases, hypercalcaemia in malignancies and osteoporosis [9]. Bisphosphonates are pyrophosphate analogues (P-O-P substance), where the binding oxygen is replaced by carbon and bound with high affinity to bone minerals (hydroxyapatite bone crystals). No enzyme has been yet known to be able to degrade the P-C-P bond, so that their metabolism is not detected [10]. During bone resorption, activated osteoclasts carry out phagocytosis of minerals bound to bisphospohonates, making it possible for their cytotoxic concentration to be accumulated in osteoclasts only [11].

It is quite clear nowadays that bisphosphonates interfere with intracellular metabolic pathways in osteoclasts necessary for normal resorptive function of these cells [12]. Nitrogen containing bisphosphonates (aminobisphosphonates) are inhibitors of mevalonate pathway enzyme, the biosynthesis pathway necessary for the synthesis of cholesterol and isoprenoid lipids (isopentenyl phyrophosphate – IPP; farnesyl pyrophosphate – FPP; geranylgeranyl phirophosphate – GGPP). The data suggest that FPP synthesis inhibition is the central mechanism through which aminobisphosphonates inhibit bone resorption induced by osteoclasts. These molecules are important signal proteins that regulate numerous functionally relevant cellular processes (morphology, "ruffled membrane" on the bone surface, endosomal transport) and survival of osteoclasts [2, 11, 12].

Ibandronate is a new drug in the aminobisphosphonate group, the third generation bisphosphonate with a hydroxyl group on R1 chain and tertiary nitrogen on R2 chain. Generally, ibandronate shares similar features with other aminobisphosphonates, but is much more potent than any of them: 2 times more potent than risedronate, 10 times than alendronate, and 50 times more potent than pamidronate. The advent of such a potent aminobisphosphonate has made it possible for the first time to synthesize an oral medication for treatment of osteoporosis to be taken once a month, promoting a new regimen of less frequent dosage with substantial prolongation of the drug-free period [2].

OBJECTIVE

The aim of the study was to investigate the efficacy of ibandronate treatment once a month in patients with decreased BMD and evaluate safety and tolerance of this treatment in the setting of everyday clinical practice.

METHODS

Study design

The ESTHER Study (Efficacy and Safety of 12 month Bonviva THERapy) is a prospective, multi-centre, observational study with one year follow-up, aimed at evaluation of efficiency and safety of ibandronate dose once a month in female patients with reduced BMD in everyday clinical practice in Serbia. Thirty-four study sites participated in ESTHER study. Before enrolment to the study, the patients gave informed consent for registration of their demographic and medical data, as well as consent for presenting the anonymized data to professional circles orally or in writing.

Enrolment criteria: Patients with decreased BMD (osteoporosis or osteopenia) and increased fracture risk, where antiresorptive treatment is indicated. Exclusion criteria: men; women with osteoporoosis due to metabolic and malignant diseases. Evaluation of efficacy: changes in T-score values after 12 months of treatment and incidence of pathological fractures during the treatment. Evaluation of safety: safety was evaluated on the basis of reported adverse events. During regular out-patient visits, a calendar on regular use of ibandronate was filled out by months. Adverse reactions were recorded specifying type of events and diagnoses were established. Discontinuation of ibandronate treatment was recorded, duration of treatment and reasons for discontinuation.

Treatment protocol

No restrictions were set in relation to duration of osteoporosis history, or presence and type of previous treatment for osteoporosis. The patients received 150 mg dose of ibandronate once monthly for 12 months, plus supplemental treatment of elemental calcium 500 mg daily and vitamin D 400 IU (average dose) daily.

Before the onset of ibandronate treatment, the following information was recorded:

I. Demographics

Age in years, reproductive status (generative period or menopause, as well as use of hormone replacement therapy-HRT) and educational level (lower than primary, primary, secondary and university education).

II. Risk factors for osteoporosis

Levels of physical activity were divided into substantial (defined as fitness exercise 3 times a week or physical labor), moderate (defined as daily walks for 1 hour outdoors) and low (less than 1 hour of walking outdoors and no physical exercise outside home). The main risk factors for osteoporosis were defined as fracture in adulthood resulting from minor trauma or fall from standing/sitting position, family history of osteoporosis in first degree relatives, low body weight (defined as body mass under 58 kg), smoking and use of oral corticosteroids for over 3 months. We also registered data on significant diseases during the last 5 years which can influence osteoporosis development (rheumatoid arthritis, connective tissue diseases, hyperthyroidism, etc.).

III. Diagnosis

Diagnosis of osteoporosis was made (1) according to WHO definition [13] based on Dual energy X-ray absorp-

tiometry-DXA on the spine and/or hip, (2) and/or based on presence of vertebral fractures, (3) and/or by skeletal radiographies. DXA measurement of BMD was not the only criterion for enrolment of patients. Decision on treatment was not based on the BMD status only, but also on the presence of risk factors for osteoporotic fracture. In patients in whom BMD was measured, values of T-score and the type of equipment used were recorded. Data on BMD were used for analysis only if the measurement was conducted less than 3 months before the onset of monthly ibandronate treatment.

IV. Previous osteoporosis treatment

Previous treatment of osteoporosis was recorded and so was the type of supplemental treatment: calcium and vitamin D, previous use of bisphosphonates (daily, weekly or intravenous bisphosphonate- pamidronate), as well as duration of previous treatment of osteoporosis.

After 12 months of ibandronate treatment, BMD scan was repeated: the site of scanning (the hip or lumbar spine), type of equipment used and value of T-score were recorded. Statistical analysis of the bone density change data included only data obtained from patients examined at the beginning and after a year of treatment on the same devices and if the same skeletal site was measured. Data on new fractures during the treatment were recorded together with time of fractures and their localization, adverse reactions, type of events and established diagnosis.

Statistical analysis

Numerical variables (age and T-score) were presented as averages, with standard deviation and range as measures of variability, while the categorical values were presented as absolute frequencies and percentages. The incidence of adverse events during the follow-up period of one year was analysed by Cochran's Q test. Student T test for paired samples was used for changes in T-score values from the baseline value to the value recorded after 12 months of follow-up. Analysis of significance of the difference in T-score from the baseline to the values after 12 months in relation to the incidence of preceding use of bisphosphonate treatment was conducted by analysis of variance for repeated measurements (General Linear Model). The rate of missing data for any of the studied features did not exceed 10%.

RESULTS

The study comprised 370 patients. The average age was 63.5±9.4 years (range 33-85 years). The distribution according to the reproductive state of the women, their educational profile, level of physical activity and risk factors is presented in Table 1.

Relevant concomitant diseases that might have affected bone metabolism (rheumatoid arthritis, connective tissue diseases, hyperthyroidism, etc.) in the last 5 years were diagnosed in 136 (37.3%) patients out of 370 enrolled in ESTHER study. Other major risk factors for osteoporosis are presented in Table 2.

The diagnosis of osteoporosis was established in 343 (92.7%) patients; in 273 (80%) patients the diagnosis was established by DXA spine and/or hip scan; and in 291 (85.6%) patients one diagnostic method was used (Table 3).

There were 214 (58.2%) new cases of osteoporosis, i.e. patients who had not received any treatment previously, while 154 (41.8%) already had received anti-osteoporotic treatment previously (Table 4). One year of treatment with ibandronate was completed by 310 (83.8%) patients, while 43 (11.6%) discontinued the treatment, and missing values were present in 17 (4.6%) patients.

BMD was measured on the lumbar spine in more than 90% of our patients. The average value of baseline T-score was -2.97±0.93 (221 patients in whom DXA image of the

Table 1. Demographic data of patients with low bone mineral density treated with ibandronate

Parameter		Number of patients
Reproductive state of women	Generative status	9 (2.5%)
	Menopause	353 (97.5%)
	Early menopause	98 (28.0%)
Hormone replacement therapy		4 (1.1%)
Educational profile	Lower than primary education	13 (3.6%)
	Elementary school	85 (23.5%)
	Secondary school	157 (43.4%)
	University education	107 (29.6%)
Physical activity	Significant	25 (6.8%)
	Moderate	214 (58.3%)
	Low	128 (34.9%)
Risk factors (in addition to menopause)	None	109 (29.5%)
	One	172 (46.5%)
	Two	78 (21.1%)
	Three and more	11 (2.9%)

Table 2. Presence of major risk factors for osteoporosis in women with low bone mineral density

Risk factors	%
Diseases affecting bone mass	37.3
Smoking	23.8
Low body weight (<58 kg)	23.2
Fractures in adulthood	22.4
Family history of fractures	21.1
Oral glucocorticoids	7.6

Table 3. Main diagnosis and diagnostic approach in patients with low bone mineral density

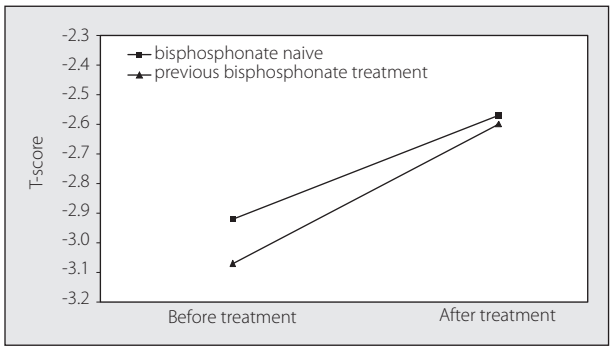
Parameter		Number of patients
Diagnosis	Osteoporosis	343 (92.7%)
	Low bone mass (osteopenia)	27 (7.3%)
Diagnostic methods used*	DXA spine/hip	273 (80.3%)
	Compression fracture	58 (17.1%)
	Radiography	63 (18.5%)
Number of diagnostic methods used	One	291 (85.6%)
	Two	44 (12.9%)
	Three	5 (1.5%)

*In some patients a few diagnostic methods were used at the same time.

Table 4. Previous osteoporosis treatment in patients with low bone mineral density

Parameter	Number of patients
Previous osteoporosis treatment	154 (41.8%)
Calcium supplements	135 (36.7%)
Vitamin D	127 (34.5%)
Bisphosphonates*	101 (27.5%)
Oral daily	53 (14.4%)
Oral weekly	52 (14.2%)
Intravenous (pamidronate)	13 (3.5%)

*Before study, patients subsequently receiving various bisphosphonates (oral daily and weekly, and intravenous)



Graph 1. T-score change in patients with low bone mineral density after 12 months of ibandronate treatment

same region before and after a year of treatment was made on the same device). After 12 months of treatment, BMD has shown highly significant improvement (t=9.793; p<0.0001), average T-score was -2.57±0.93 (increase of 13.42%).

Average baseline T-scores in the bisphosphonate naïve subgroup and in the subgroup with previous bisphosphonate treatment were -2.92±0.97 and -3.07±0.84, respectively. Average T-scores after 12 months in the bisphosphonate naïve subgroup and in the subgroup with previous bisphosphonate treatment were -2.57±0.94 and -2.60±0.93, respectively. Both subgroups significantly increased their T-score (F=88.750; p<0.0001), but the difference between the increased BMD of the compared groups was not significant (F=1.680; p>0.05) (Graph 1).

No adverse events were reported in 84.1% (311), while 10.5% (39) of the patients reported an adverse event, for 5.4% (20) patients the adverse event information was missing. Analysis of distribution of adverse events by the months of treatment showed a statistically significant fall of the adverse event incidence over the one year of follow-up (Q=42.193; p<0.0001), from 6% (21) at baseline to 1% (3) after 12 months. In the course of 12 months of follow-up, new fractures were recorded in 1.7% (6) of patients: 3 patients with wrist fractures and 3 with vertebral fractures.

DISCUSSION

The aim of our study was to collect the results of ibandronate efficacy and safety in patients with decreased BMD in everyday clinical practice.

The great majority of patients (92.7%) were diagnosed with osteoporosis and 97.5% of them were post-menopausal. Only few cases were women in reproductive age (2.5%) who received glucocorticoids or those with osteopenia (7.3%), but with significant fracture risk factors. Demographic data revealed that ibandronate was prescribed in educated patients (70% of the patients had secondary and university education). Level of physical activity in majority of patients (58%) was moderate, and poor in more than a third of patients (35%). This fact could reveal an important area for our future preventive activities.

Risk factors for osteoporosis, apart from menopause, were present in 70.5%, and the remaining 29.5% were risk-factor free. Similar distribution of risk factors have been reported recently by Perez et al [14], which suggests the importance of menopause and additional risk factors for development of the disease.

It is encouraging that in a high percentage (80%) of our patients the diagnosis was established timely and correctly on the basis of DXA scan of the spine and/or hip; in 18.5% of the patients the diagnosis was based on x-ray findings, which is an unreliable diagnostic method; or by crush fracture (in 17%), suggesting a late diagnosis. Results of the study have shown that ibandronate was mostly used in newly diagnosed (58%), and in bisphosphonate naïve patients (73% patients). Previous usage of bisphosphonates was recorded in 27% of patients.

Improvement of T-score after a year of treatment was highly significant, despite the fact that 37.3% of patients in our sample had accompanying concomitant diseases (rheumatoid arthritis, systemic disease of connective tissue, endocrine diseases, or use of glucocorticoids) which can worsen the bone loss in osteoporosis.

The improvement was significant and with similar pattern both in the initially bisphosphonate naïve patients and in the group of patients previously receiving daily/weekly/intravenous bisphosphonate. These results are in accordance with the previously reported results of ibandronate randomized controlled trials and meta-analyses [15, 16, 17].

Poor compliance with the prescribed therapy particularly in cases of chronic "clinically silent" diseases is a serious and widespread problem in clinical practice [18, 19]. In our study, adherence with treatment was quite satisfactory: after 12 months 83.8% of patients were still on ibandronate treatment. Early discontinuation of treatment was reported in 11.6% patients (usually because of the treatment cost, and in individual cases due to gastric intolerance or concomitant diseases). This level of adherence is above the reported rates for weekly bisphosphonates [20], which implies that less frequent dosing could improve adherence and satisfaction [21] in treatment of osteoporosis. It is also expected that good adherence can influence better BMD response and lower fracture rates. In our trial, BMD increase was significant and fracture incidence during 12 month treatment was 1.7%, which coincides with the recently published data of more than 64,000 patients in USA, where the incidence of fractures over 12 months was less than 2% [22].

Studies so far illustrate that the incidence of adverse events with daily and intermittent ibandronate is similar to

placebo [15]. In our study, 84% of patients did not report any adverse events. There were no adverse events that would require termination of treatment. Individual cases of gastrointestinal complaints were recorded (heartburn, nausea, gastric pain and vomiting). Analysis of distribution of the reported adverse events by the months (in 10.5% of the subjects) shows a statistically significant fall in the incidence of adverse events over time, from 6% in the first month to 1% after 12 months ($Q=42.193$; $p<0.0001$) coinciding with the data reported in reference literature.

Extension of the drug-free interval to a month with ibandronate is made possible by parameters strength and its tolerance [23]. Reginster et al. report that the possibility of intermittent use of bisphosphonate is important for improvement of the notorious suboptimal persistence and compliance over two years of osteoporosis treatment. It is also beneficial because of lower potential for bisphosphonate induced irritation of the gastrointestinal tract, primarily the oesophagus. There is a solid body of evidence that daily prolonged contact of the esophagus with bisphosphonate tablets or reflux of acid stomach content with bisphosphonate may lead to oesophagus irritation. Since the oesophageal mucosis needs 5 days to recover, on the average, prolongation of the dosing interval beyond a week gives additional time for this recovery and impairs the risk of potential oesophageal irritation [20].

CONCLUSION

Significant increase of T-score was achieved after 12 months of treatment with ibandronate once monthly, both in bisphosphonate naïve, and in patients previously treated by other bisphosphonates. Treatment safety was good without any serious adverse events requiring termination of treatment. Usual adverse events characteristic of this class of drugs occurred in the first month, with a falling trend over the subsequent treatment period.

NOTE

The results of this paper were presented as oral presentation at The Annual Meeting of Rheumatologists of the Republic of Serbia, Ivanjica, September 26, 2008. Abstract has been published in Acta rheumatologica Belgradensia 2008; 38(Suppl 1):23.

ACKNOWLEDGMENT

We gratefully acknowledge the generous support of Roche d.o.o. Belgrade in this study, from the main concept, gathering the investigators, designing and printing CRFs for all patients, collection of completed data and assistance in processing thereof. They succeeded to draw together a large number of Serbian doctors in 34 centres to conduct the study successfully.

We particularly appreciate contribution of each of the doctors participating in the ESTHER study group from all 34 centres in Serbia who made additional effort, alongside their extensive daily routine, and committed their time and energy to register and monitor precisely all the required parameters.

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Ефикасност и сигурност лечења болесница са смањеном минералном густином кости једномесечном дозом ибандроната – студија *ESTHER*

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КРАТАК САДРЖАЈ

Увод Од остеопорозе углавном оболевају жене у менопаузи. У клиничкој пракси је значајно откривање и адекватно лечење болесница с факторима ризика за преломе. Лечење је индивидуално, а да би се спречили преломи, потребно је одабрати терапију која ће омогућити добру и дуготрајну сарадњу болесница. Досадашње студије показују да је редовно и дуготрајно узимање лека недељном применом бисфосфоната неадекватно (мање од 43% болесница остаје на лечењу након годину дана). Синтезом ибандроната, моћног аминобисфосфоната, први пут је омогућено лечење остеопорозе једном таблетом месечно.

Циљ рада Циљ студије је било испитивање ефикасности, сигурности и подношљивости ибандроната примењеног једном месечно код жена са смањеном минералном густином кости.

Методе рада Проспективна студија је изведена у 34 центра у Србији, а обухватила је 370 жена са смањеном минералном густином кости које су лечене ибандронатом једном месечно. Испитани су: демографски подаци, фактори ризика за остеопорозу, начин постављања дијагнозе, претходно лечење остеопорозе и пратеће болести. Ефикасност лечења је праћена променом индекса Т након годину дана. Забележени су подношљивост лечења, компијанса и нежељени догађаји.

Резултати Испитивану групу је чинило 97,5% жена у менопаузи, од чега 92,7% с остеопорозом. Код 80% болесница дијагноза је постављена мерењем *DEXA*. Код више од 90% испитаница установљена је незадовољавајућа физичка активност, док су код 70%, осим менопаузе, уочени и додатни фактор ризика за остеопорозу. После дванаест месеци лечења забележени су стопостотна комплијанса (код 84% испитаница) и значајно смањење губитка коштаног ткива (p<0,0001), независно од ранијег лечења аминобисфосфонатима. Болеснице су добро подносиле терапију, а тешких нежељених реакција није било. Гастроинтестиналне тегобе дијагностиковане у првом месецу лечења (6%) значајно су се смањиле (p<0,0001) дванаест месеци касније (1%).

Закључак Након годину дана лечења ибандронатом болесница са смањеном густином кости наступило је значајно побољшање коштане густине, уз добру подношљивост примењене терапије и одличну сарадњу болесница током лечења.

Кључне речи: остеопороза; минерална густина кости; фактори ризика; бисфосфонати; ибандронат

Примљен • Received: 21/09/2009 **Прихваћен • Accepted:** 10/11/2009