Clinical Effects of a 6-Month Treatment Course of Ibandronate, Vitamin D, and Calcium in Postmenopausal Women from Central America: Results of a Multinational, Prospective Pilot Study

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Key Words
Osteoporosis · Central America · Ibandronate · Vitamin D · Calcium

Abstract
Background/Aims: To explore the effects of ibandronate plus a supplementation of vitamin D and calcium on bone mineral density (BMD) and health-related quality of life (HRQoL) in a sample of postmenopausal women from Central America. Secondarily, factors related to the magnitude of improvements in BMD after treatment were investigated. Methods: Postmenopausal women with idiopathic osteoporosis or at risk of developing it, who were going to start treatment with ibandronate 150 mg once a month plus daily supplementation with vitamin D 400–800 IU and calcium 500–1,000 mg, were followed up for 6 months. BMD, HRQoL (mini-Osteoporosis Quality of Life Questionnaire), and treatment adherence (Morisky scale) were studied before and after treatment. Results: Four hundred and twenty-five women were assessed at baseline, and 308 (72%) were reassessed at month 6. Lumbar spine, proximal femur, and hip BMD increased by 3.35 ± 0.75, 1.88 ± 0.50, and 2.75 ± 0.32%, respectively (p < 0.001 for all). HRQoL total score and emotional functioning, symptoms, physical function, and leisure subscores improved by 26–49% (p < 0.01 in all cases). Lower body mass index, younger age at menopause, use of corticoids, and higher adherence were significantly and independently associated with a greater improvement in lumbar spine BMD (logistic regression).
Introduction

Osteoporosis is a chronic, silent disease characterized by loss of bone mineral density (BMD) and structural abnormalities, which leads to an increased risk of bone fractures [1]. Osteoporosis affects about 30% of postmenopausal women [1]. Bisphosphonates are the most frequently used antiresorptive pharmacological therapy [2]. Ibandronate is a third-generation nitrogen-containing bisphosphonate with recognized antiresorptive efficacy in several international, randomized, double-blind, controlled trials [3–9]. To the best of our knowledge, antiresorptive activity of the drug has never been explored in Central America, even though the drug is widely used in the region. This is not trivial, as there are differences in the characteristics of osteoporotic women around the globe [10, 11], suggesting that the clinical effects of the antiresorptive agents might not be similar in all regions. Furthermore, in modern society, integrative therapy is the best way for most diseases [12], and, therefore, ibandronate might be used in conjunction with vitamin D and calcium to enhance its efficacy.

We set out this study to explore the effects of a 6-month treatment course with ibandronate plus a supplementation of vitamin D and calcium on BMD and health-related quality of life (HRQoL) in a sample of patients from Central America. Secondarily, factors related to the magnitude of improvements in BMD were investigated.

Methods

Study Design

This was a 6-month prospective study conducted in Honduras, Guatemala, and El Salvador. The study was approved by the Independent Ethics Committee for Pharmacological Studies (Buenos Aires, Argentina). All patients gave informed consent before entering the study. All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments (Clinicaltrials.gov ID: NCT02635997).

Sample

Postmenopausal women with a diagnosis of osteoporosis or with risk factors and who were going to start treatment with ibandronate 150 mg monthly plus a daily supplementation with vitamin D and calcium were selected for participation. Patients with secondary causes of osteoporosis were excluded.

A power analysis determined that 350 patients would be needed to show changes after treatment of ≥1.5% in BMD. The sample size was then fixed to 420 women to account for a possible 20–25% dropout rate.

Antiresorptive Treatment

All participants received treatment with ibandronate 150 mg once a month plus daily supplementation with vitamin D₃ 400–800 IU and calcium 500–1,000 mg.
Study Procedures

Patients were studied at baseline and after a 6-month treatment course. BMD was measured in the lumbar spine and proximal femur by means of dual-energy X-ray absorptiometry (GE Lunar DPX-PRO). In a minority of patients, BMD at the hip and wrist was also measured. According to WHO recommendations, osteopenia was defined when T-scores were between −1.0 and −2.5, whereas lower values were considered osteoporosis.

HRQoL was studied by the mini-Osteoporosis Quality of Life Questionnaire (mini-OQLQ) [13]. Total and subdomain scores related to emotional functioning (items No. 1 and 2), symptoms (items No. 4 and 9), physical function (items No. 3 and 5), and leisure (items No. 6 and 8) were calculated. Lower scores represented worse quality of life. The activity of daily life subdomain score could not be calculated, as more than 50% of participants did not use vacuum cleaners (item No. 10).

Adherence to antiresorptive therapy at month 6 was evaluated by the Morisky scale [14]. Briefly, this is a 4-item survey about adherence to medications. Patients have to inform if they miss doses, if they are careless with dose timing, and if they stop medication when feeling worse or better. Positive answers are summed, and the total score reflects the likelihood of nonadherence.

Statistical Analysis

Change from baseline in study outcomes was assessed by means of paired t tests. For the analysis of factors related to the magnitude of improvement in BMD, changes in lumbar and femoral BMD were dichotomized to their medians. Differences between patients above or below the median were analyzed by the t test or χ² test. All significant variables were entered in a stepwise logistic regression analysis. Statistical analysis was performed with IBM SPSS version 23 (USA).

Results

Four-hundred and twenty-five patients were recruited for this study. The mean (± SD) age was 63.7 ± 9.9 years, and the mean body mass index was 28.3 ± 6.6. The mean age at menopause was 46.2 ± 5.2 years, and 73% of women had natural menopauses. Seventeen percent of women were on hormone replacement therapy, while 7% had received glucorticoids during their life for a mean period of 2.3 ± 2.6 years. Previous bone fractures were reported by 21% of participants. All patients showed reduced BMD levels on at least one location. At the lumbar spine, 55% showed osteopenia and 30% osteoporosis. At the femur, osteopenia was present in 47% of patients and osteoporosis in 9%. Finally, percentages of women with osteopenia or osteoporosis were 37 and 7% at the hip and 39 and 11% at the wrist.

Out of the 425 women, 308 could also be evaluated at month 6 (72%). Incident bone fractures were observed in 9 women (3.3%). Nonadherence to ibandronate was registered in 48 women (15%), and adverse events were observed in 20 cases (7%), the most frequent ones being epigastralgia and gastric pain. As shown in table 1, BMD was significantly increased at the lumbar spine, femoral neck, and hip, but not at the wrist. Similarly, significant improvements in all HRQoL scores were observed.

Median values for % change in BMD in the lumbar spine were 2.26 and 1.46% in the femoral neck. Differences between women with changes above or below the median value for the lumbar spine are shown in table 2. Significant and independent predictors of greater change were lower weight at baseline, younger age at menopause, use of corticoids, and a higher degree of adherence to treatment (logistic regression). Conversely, only BMD at baseline was related to greater improvement in femoral BMD (data not shown).
**Table 1.** BMD and HRQoL before and after a 6-month treatment course with ibandronate, vitamin D, and calcium

|                          | Baseline  | 6 months  | 6-month-to-baseline difference | % change |
|--------------------------|-----------|-----------|-------------------------------|----------|
| **BMD, g/cm²**           |           |           |                               |          |
| Lumbar spine             | 0.88±0.14 | 0.90±0.14**| 0.02±0.07                     | 3.35±13.16|
| Femoral neck             | 0.81±0.10 | 0.83±0.15**| 0.02±0.08                     | 1.88±7.72 |
| Hip**                    | 0.87±0.13 | 0.89±0.13**| 0.02±0.02                     | 2.75±2.46 |
| Wristb                   | 0.52±0.11 | 0.52±0.09**| -0.01±0.02                    | -1.49±4.21|
| **Mini-OQLQ score**      |           |           |                               |          |
| Total                    | 0.7±0.2   | 0.8±0.2**  | 0.1±0.2                       | 31.4±67.0 |
| Emotional functioning    | 6.8±3.3   | 8.5±2.5**  | 1.7±2.8                       | 49.3±102.2|
| Symptoms                 | 8.7±3.0   | 10.3±2.1** | 1.5±2.6                       | 38.7±95.2 |
| Physical function        | 7.7±3.3   | 8.8±2.7**  | 1.1±3.3                       | 27.0±90.7 |
| Leisure                  | 9.1±2.9   | 10.3±2.1** | 1.2±2.3                       | 26.1±60.4 |

Means ± SD are shown. ** p < 0.01 versus baseline (paired t test).

a Available in 57 subjects. b Available in 28 subjects.

**Table 2.** Factors related to greater change in lumbar spine BMD

|                          | ≤2.26% (n = 152) | >2.26% (n = 152) | Logistic regression OR (95% CI) |
|--------------------------|-----------------|-----------------|-------------------------------|
| Age, years               | 64.4±9.5        | 62.8±9.4        |                               |
| Body mass index          | 29.3±8.0        | 27.0±4.5*       | 0.94 (0.89–0.99)              |
| Age since menopause, years | 47.3±4.9       | 45.8±5.3*       | 0.94 (0.89–0.98)              |
| Cause of menopause       |                 |                 |                               |
| Natural                  | 113 (76)        | 103 (69)        |                               |
| Surgical                 | 35 (24)         | 46 (31)         |                               |
| Smoking                  |                 |                 |                               |
| Never                    | 142 (95)        | 139 (92)        |                               |
| Smoker                   | 2 (1)           | 1 (1)           |                               |
| Former smoker            | 6 (4)           | 11 (7)          |                               |
| Physical activity        |                 |                 |                               |
| Every day                | 27 (18)         | 39 (26)*        | NI                            |
| 4–6 days/week            | 11 (7)          | 10 (7)          |                               |
| 1–3 days/week            | 11 (7)          | 19 (13)         |                               |
| Sporadically             | 39 (26)         | 45 (30)         |                               |
| Never                    | 63 (42)         | 39 (26)         |                               |
| Hormonal replacement therapy | 22 (14)      | 30 (20)         |                               |
| History of fracture at baseline | 36 (24)   | 23 (15)*        | NI                            |
| Previous use of corticoids | 5 (4)          | 14 (11)*        | 3.57 (1.17–10.91)             |
| Spine BMD at baseline, g/cm² | 0.90±0.13    | 0.86±0.14*      | NI                            |
| Adherence to ibandronate | 0.4±0.9        | 0.2±0.6*        | 0.67 (0.46–0.97)              |
| Adverse events           | 11 (8)          | 6 (4)           |                               |

Data shown are means ± SD or n (%), unless otherwise stated. NI = Not included in the final logistic regression model. * p < 0.05 versus women with changes below the median values (t test or χ² test). Variables showing significant differences were entered in a stepwise logistic regression analysis.
Conclusions

Ibandronate efficacy and safety have been demonstrated in several clinical trials [3–9]. Even if this drug is commonly used in Central America, to the best of our knowledge, its clinical effects have never been studied before in patients from this region. In this study, we observed significant increments in BMD and HRQoL after a 6-month treatment course with ibandronate in combination with vitamin D and calcium supplementation. Interestingly, the mean improvements in lumbar spine and proximal femur BMD (i.e. 3.35 and 1.18%, respectively) are in line with results from international clinical trials [4, 8], suggesting that clinical effects of ibandronate in Central American postmenopausal women might be similar to those from other parts of the world. These results might have also depended on the administration of the bisphosphonate with vitamin D and calcium, which may have helped to boost the clinical effects of the drug.

Before further discussion, some limitations of this study must be mentioned. In the first place, a placebo effect cannot be ruled out as we employed an open-label, uncontrolled design. A double-blind, randomized, placebo-controlled trial would have accounted for this bias, but it was considered unfeasible in the region, due to budget, logistic, and ethical constraints. Because of the same reasons, follow-up could not be extended beyond 6 months.

Our study also had some strengths. Firstly, it was designed to be as inclusive as possible, thus probably making results easily applicable to the target population. Another strength of our study was the evaluation of HRQoL by means of the mini-OQLQ. Effects of ibandronate on HRQoL have seldom been assessed [15, 16]. Our results suggest that all aspects of QoL may improve with ibandronate, which should be a primary goal of antiresorptive therapy according to some authors [17].

We could also analyze which factors were associated with a better outcome at month 6. Lower weight, younger age at menopause, history of corticoid use, and higher adherence were independently and significantly associated with a better outcome. The first three factors are probably related to a more severe disease, and, thus, it may be logical to observe a greater effect with the treatment. The effects of a lack of adherence are also self-evident, as drugs are not effective in patients who do not take them [18]. Nonadherence appears to be very common in osteoporosis, with a systematic review of 14 studies suggesting that the rate of persistence on antiresorptive therapy may be as low as 18%. In our study, we observed that 85% of women adhered to treatment, a better-than-expected result probably explained by the short-term nature of the follow-up and the effect of being part of a cohort. Interestingly, our results suggest that nonadherence was related to worse outcomes and, thus, suggest that physicians should discuss with their patients the importance of adhering to the antiresorptive therapy.

In summary, in this open-label, single-arm study, conducted in Central America, significant improvements in BMD at the lumbar spine, proximal femur and hip, as well as in HRQoL, were observed with a 6-month treatment course of ibandronate plus supplementation with vitamin D and calcium. These results suggest that the clinical effect of ibandronate in Central American postmenopausal women may be comparable to those of the rest of the world, which should be further explored by randomized, double-blind, controlled trials. Results also showed that nonadherence impacted negatively on BMD improvement. Therefore, physicians should insist on the importance of adhering to the antiresorptive treatment in order to enhance the clinical effectiveness of the drugs.
Appendix

Study Group

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Disclosure Statement

Arturo Arellano is an employee of Recalcine Pharmaceutical Corporation. María Verónica Rey is CEO of Etymos. Carmen Elena Gutiérrez, Helga Codina, Cesar Benjamin Matamoros Pinel, Edin Hidalgo, and Santiago Perez-Lloret have nothing to declare. The authors alone are responsible for the content and writing of the paper.

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