

ORIGINAL ARTICLE

Patient preference for once-monthly ibandronate versus once-weekly alendronate in a randomized, open-label, cross-over trial: the Boniva Alendronate Trial in Osteoporosis (BALTO)

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ABSTRACT

Objective: Ibandronate, a potent nitrogen-containing bisphosphonate, can be administered with extended interval dosing. Patient preferences were assessed for once-monthly versus once-weekly bisphosphonate treatment using a previously developed, open-label, cross-over trial design.

Research design and methods: This was a 6-month, prospective, randomized, open-label, multi-center study with a two-period and two-sequence cross-over treatment design. After screening, eligible patients (postmenopausal women with osteoporosis) were randomized to once-monthly ibandronate 150 mg followed by once-weekly alendronate 70 mg for a

total of 6 months (Sequence A) or once-weekly alendronate followed by once-monthly ibandronate for a total of 6 months (Sequence B). The primary objective was to evaluate patient-reported preference for either the once-monthly ibandronate regimen or the once-weekly alendronate regimen based on responses to a preference questionnaire.

Results: A total of 342 patients were enrolled into this study (Sequence A, 170; Sequence B, 172). In the primary analysis of patient preference, 71.4% of women selected once-monthly ibandronate and 28.6% of women selected once-weekly alendronate. Overall, 66.1% preferred the once-monthly ibandronate

regimen to the once-weekly alendronate regimen (26.5%) and 7.4% of participants stated no preference for either regimen. The preference rate for once-monthly ibandronate was statistically significant ($p < 0.0001$). 'Ease of following a treatment regimen for a long time' was the most common reason given for patient preference for both the once-monthly ibandronate (61%, 169/276) and once-weekly alendronate (25%, 70/276) regimens. Additionally, 17% (47/276) of patients who preferred once-monthly ibandronate chose 'it

is easier to tolerate side effects' as did 4.3% (12/276) of patients who preferred alendronate. Significantly more women found once-monthly ibandronate to be more convenient ($p < 0.0001$).

Conclusions: Significantly more women with postmenopausal osteoporosis preferred once-monthly ibandronate therapy to once-weekly alendronate therapy, and found the once-monthly regimen to be more convenient. Ease of following a treatment regimen for a long time was the most common reason given for the patients' preferences.

Introduction

Primary osteoporosis is a chronic, progressive, and age-related bone disease affecting approximately 44 million Americans^{1,2}. It is characterized by low bone mass and structural deterioration of bone tissue which causes bones to become more fragile over time, increasing their susceptibility to fracture. Approximately 55% of individuals 50 years of age and over are at risk or may have evidence of osteoporosis^{1,2}. Although osteoporosis itself is a silent disease, its long-term clinical consequences, notably the occurrence of fractures, can impact a patient's quality of life, morbidity, and even mortality. One in two women and one in four men over 50 years of age will sustain an osteoporosis-related fracture during their lifetime¹.

Bisphosphonates are the cornerstone of therapy for the treatment of postmenopausal osteoporosis (PMO). As a class, bisphosphonates work by reducing bone turnover, which leads to an increase in bone density and preservation or improvement in bone architecture³⁻⁸. In clinical trials, these pharmacologic effects have been measured through improvements in the efficacy endpoints of bone mineral density (BMD) and bone turnover markers (BTMs). The clinical benefits of bisphosphonate therapy, including a significantly reduced risk of vertebral and nonvertebral fractures, also have been demonstrated in clinical trials^{6,9-16}. The three bisphosphonates currently available for oral use in the US are risedronate, alendronate, and ibandronate, all of which are nitrogen-containing bisphosphonates. Both risedronate and alendronate can be administered as once-daily doses or once-weekly doses for the treatment and prevention of PMO. Ibandronate is a new and potent bisphosphonate that has been shown to be effective in preventing and treating PMO when administered as a once-monthly dose¹⁷.

As is common with respect to chronic conditions, decisions regarding osteoporosis medications are largely the responsibility of the treating physician. However, clinicians are becoming increasingly aware of the importance of incorporating patient preferences into the decision-making process¹⁸. Treatment adherence

is a serious problem in patients with chronic diseases such as osteoporosis¹⁹⁻²², in which the benefits of treatment, along with the potential consequences of long-standing disease, may not be sufficiently apparent to asymptomatic patients. Given these and other barriers (such as the lack of apparent and immediate treatment benefits, polypharmacy, and co-morbidities), involving patients in treatment decisions and offering them a choice of therapy may benefit treatment adherence and, ultimately, treatment success²³. There is supportive evidence that patients with osteoporosis prefer less frequent dosing with bisphosphonates. In two independent studies of women with PMO, the majority of participants expressed a preference for a once-weekly regimen of alendronate compared with a once-daily regimen^{23,24}. In addition to preference data, a recent analysis of a large medical claims database has demonstrated patient adherence to bisphosphonate treatment to be better with weekly therapy than with daily therapy, albeit adherence to therapy overall continues to be suboptimal²².

Although once-weekly dosing has contributed to improve osteoporosis care, it is anticipated that further advances in convenience may be achieved with dosing regimens featuring extended drug-free intervals; this improvement in the dosing regimen may ultimately improve patient compliance and persistence with oral bisphosphonate treatment²⁶. A randomized, open-label, multicenter trial was conducted in women with PMO in order to evaluate patient-reported preferences for either the once-monthly dosing regimen of ibandronate or the once-weekly dosing regimen of alendronate. Patient responses concerning reasons for their preferences, the convenience of both regimens, and safety outcomes also were evaluated.

Methods

Study design and treatment interventions

This was a 6-month, prospective, randomized, open-label, multi-center study with a two-period and two-sequence cross-over treatment design. This study is

similar in design to a previous trial which demonstrated that patients preferred once-weekly over once-daily alendronate²⁴. Preference studies of products that focus primarily on external features like ease of use, frequency of dosing, or mode of administration generally are open-label, as the nature of the determinant of preference being evaluated precludes a double-blind design.

The study was conducted at 48 centers and enrolled ambulatory women with PMO who were either bisphosphonate naïve or had discontinued their daily bisphosphonate therapy for at least 3 months prior to study entry. Informed consent was obtained from all study participants. The study protocol and all materials distributed to patients were approved by an Independent Ethics Committee or Institutional Review Board. The study was initiated in March 2004 and completed in December 2004.

Women with abnormalities of the esophagus, which delayed esophageal emptying, were excluded. Eligible patients were randomized to receive either once-monthly ibandronate 150 mg followed by once-weekly alendronate 70 mg for a total of 6 months (Sequence A) or once-weekly alendronate followed by once-monthly ibandronate for a total of 6 months (Sequence B). Central randomization was used to ensure similar distribution of patients by age and prior bisphosphonate use (bisphosphonate-naïve or lapsed daily users). There was no washout period between the two treatment periods. Patients received the other drug at the cross-over visit, which was held after 3 months (Sequence A) or 12 weeks (Sequence B) after randomization (Figure 1). A follow-up period of 15 days after treatment completion was included for collection of additional safety information.

Both study medications were to be taken in the morning after an overnight fast (6 h or more); patients were to take the medications while in an upright position (sitting or standing) and were to refrain from lying down and eating for 60 min after taking ibandronate

and 30 min after taking alendronate. All patients received the appropriate dosing and administration instructions for the study medications, and were instructed to take supplemental calcium and vitamin D tablets with the evening meal. Doses of supplemental calcium and vitamin D were recommended by the investigator–physician. Patient compliance was assessed by maintaining records of drugs dispensed versus drugs returned on the case report form. Adverse events and laboratory safety parameters also were assessed and information on clinically relevant concomitant medications was recorded by the study investigator.

All patients were requested to complete the Preference Questionnaire at the end of the study or when they withdrew from the second treatment period if they had taken at least one dose of each medication. The Preference Questionnaire was adapted from an existing questionnaire used in a previous osteoporosis study²⁴ and validated by the MEDTAP Institute Inc (Bethesda, MD) (Figure 2). The questions were tested for appropriateness through one-on-one patient interviews and modified if necessary to improve clarity, logic, or comprehension.

The primary objective of the study was patient preference for either the once-monthly ibandronate regimen or the once-weekly alendronate regimen among patients expressing a preference in the preference questionnaire. The secondary objective of the study was to assess the convenience of the once-monthly ibandronate regimen compared with the once-weekly alendronate regimen.

Statistical analysis

It was estimated that 62% of patients would prefer monthly versus weekly dosing. A total of 229 patients were needed to show a statistically significant preference of at least 58% for monthly dosing with a power of 90% using a 5% two-sided significance level. It was assumed

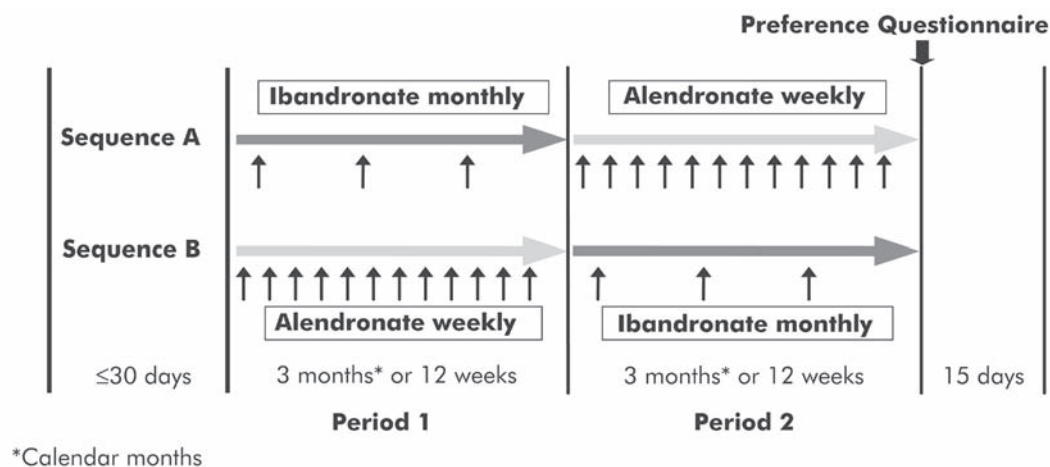


Figure 1. Study design and randomization schedule. *Calendar months

<p>1. Which dosing schedule do you prefer? (check <input type="checkbox"/> one box only)</p> <p><input type="checkbox"/> I prefer the once-monthly dosing schedule. ➤ Go to Question 2</p> <p><input type="checkbox"/> I prefer the once-weekly dosing schedule. ➤ Go to Question 3</p> <p><input type="checkbox"/> I do not prefer one dosing schedule over the other dosing schedule. ➤ Go to Question 4</p> <p>2. If you prefer the once-monthly dosing schedule, please check all the statements you agree with. (check <input type="checkbox"/> all that apply)</p> <p><input type="checkbox"/> The once-monthly dosing schedule causes less stomach discomfort.</p> <p><input type="checkbox"/> It is easier to tolerate side effects overall with the once-monthly dosing schedule.</p> <p><input type="checkbox"/> The once-monthly dosing schedule fits better into my lifestyle.</p> <p><input type="checkbox"/> It would be easier to follow the once-monthly dosing schedule for a long period of time.</p> <p><input type="checkbox"/> I do not agree with any of the above. ➤ Go to Question 4.</p> <p>© F. Hoffmann-La Roche Ltd., 2005</p>	<p>3. If you prefer the once-weekly dosing schedule, please check all the statements you agree with. (check <input type="checkbox"/> all that apply)</p> <p><input type="checkbox"/> The once-weekly dosing schedule causes less stomach discomfort.</p> <p><input type="checkbox"/> It is easier to tolerate side effects overall with the once-weekly dosing schedule.</p> <p><input type="checkbox"/> The once-weekly dosing schedule fits better into my lifestyle.</p> <p><input type="checkbox"/> It would be easier to follow the once-weekly dosing schedule for a long period of time.</p> <p><input type="checkbox"/> I do not agree with any of the above. ➤ Go to Question 4.</p> <p>4. Which dosing schedule is more convenient? (check <input type="checkbox"/> one box only)</p> <p><input type="checkbox"/> The once-monthly dosing schedule is more convenient</p> <p><input type="checkbox"/> The once-weekly dosing schedule is more convenient</p> <p><input type="checkbox"/> The once-monthly dosing schedule and the once-weekly dosing schedule are equally convenient</p>
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Figure 2. Patient preference questionnaire

that 20% of patients would express no preference and that 15% would not complete the study. Adjusting for these conditions, 338 patients were needed for randomization (169 patients per sequence). Statistical testing was performed against the null hypothesis, which assumed a preference rate of 50% for once-monthly ibandronate for each treatment sequence. Significance was assessed using Gart's test²⁷ (subjects with no preference were excluded from the analysis) and the Prescott test²⁸, which includes all data (preference and no preference data). Both tests were applied taking the order in which the treatments were received into account.

Results

Patient disposition and baseline characteristics

A total of 342 patients were enrolled into the study across 48 centers in the US; 170 patients were randomized to Sequence A (Period 1, ibandronate; Period 2, alendronate) and 172 patients were randomized to Sequence B (Period 1, alendronate; Period 2, ibandronate). Forty-eight patients withdrew from the study across all treatment periods (22 [6.9%] while receiving ibandronate and 26 [8.1%] while receiving alendronate). Adverse events were the most common reason for discontinuation during both treatment periods.

Overall, 335 of 342 (98%) patients were included in the safety analysis population (defined as patients who had received one dose of the study medication and had one follow-up data endpoint) and 298 of 342 (87%) were included in the modified intent-to-treat (mITT) population (Sequence A, 149; Sequence B, 149). The mITT population included patients who received at

least one dose of the study medication in each treatment period and stated a preference for one of the regimens or stated that they had no preference. There was no per-protocol population defined in this study. The major reason for exclusion of patients from both study populations was 'no medication taken'.

Demographic data for the safety population are presented in Table 1; the mean age of the patients was 64 years (range 30–87 years), while the majority were under 75 years of age (Sequence A, $n = 133$; Sequence B, $n = 132$). Patients in Sequence A and Sequence B were well matched with regard to the mean age, weight, height, age at menopause, and time since menopause at screening. The majority of patients ($\geq 91\%$) were Caucasian.

Risk factors for osteoporosis and fractures were generally comparable for patients entering Sequences A and B. More patients randomized to Sequence A reported a history of fracture as an adult (42.0% vs. 34.9%), and fewer patients randomized to Sequence A had a history of fragility fractures in a family member (18.3% vs. 23.5%). More than 70% of patients in each treatment sequence had not experienced a low trauma fracture since the age of 45 years. Few patients reported a previous low-trauma wrist, spine, hip, or other fracture, and the incidence of these fractures was slightly higher for Sequence A compared with Sequence B (27.8% vs. 21.7%). The incidence of low-trauma spine fracture only was more common in Sequence B compared with Sequence A (25.0% vs. 14.9%).

The most common medications for osteoporosis taken by the patients at any time prior to study enrollment were hormone replacement therapy (Sequence A, 27.8%; Sequence B, 34.3%), bisphosphonates (Sequence A, 9.5%; Sequence B, 10.2%), and selective estrogen receptor modulators (Sequence A, 6.5%; Sequence B, 4.2%). Less than 1% of women were receiving estrogen

Table 1. Patient demographics

Variable	Sequence A (n = 169)	Sequence B (n = 166)	Total (n = 335)
Age (years)			
n	169	166	335
Mean	63.9	64.1	64.0
Range	41–87	30–86	30–87
Height (in)			
n	168	166	334
Mean	63.5	62.8	63.2
Range	49–69	47–69	47–69
Weight (lbs)			
n	168	166	334
Mean	152.1	150.7	151.4
Range	97–285	91–260	91–285
Race			
Caucasian/white	159 (94.1%)	151 (91.0%)	310 (92.5%)
Black	1 (0.6%)	8 (4.8%)	9 (2.7%)
Oriental	3 (1.8%)	1 (0.6%)	4 (1.2%)
Other	6 (3.6%)	6 (3.6%)	12 (3.6%)
Highest level of education			
Elementary school	6 (3.6%)	2 (1.2%)	8 (2.4%)
High school	62 (36.9%)	64 (38.6%)	126 (37.7%)
Some college	49 (29.2%)	49 (29.5%)	98 (29.3%)
College	38 (22.6%)	34 (20.5%)	72 (21.6%)
Postgraduate degree	13 (7.7%)	17 (10.2%)	30 (9.0%)
Missing	1	0	1
Current occupation			
Working	83 (49.1%)	73 (44.0%)	156 (46.6%)
Not working	86 (50.9%)	93 (56.0%)	179 (53.4%)

therapy during the study. The majority of patients (89.3%) had no prior exposure to bisphosphonates at baseline, while approximately 10% were prior daily bisphosphonate users.

Patient preference

Most patients (92.6%) declared a preference between the two regimens; only 22 of 298 (7.4%) patients reported no preference at the end of the study. For all patients who reported a preference for a treatment regimen, the once-monthly ibandronate regimen was preferred by 71.4% (197/276) and the once-weekly alendronate regimen was preferred by 28.6% (79/276). The preference for once-monthly ibandronate was statistically significant ($p < 0.0001$). The sequence in which the medications were taken did not affect patient preference (Gart-order-effect, $p = 0.1855$). When preference data for all patients (including those who did not express a preference for any treatment regimen) were analyzed, 66.1% (197/298) preferred once-monthly ibandronate and 26.5% (79/298) preferred once-weekly alendronate. Again, the preference rate for once-monthly ibandronate was statistically significant ($p < 0.0001$) (Figure 3). Preference data were analyzed also for various subpopulations specified in the study

protocol a priori. Results for these subpopulations, excluding patients who did not express a preference for any treatment, are presented in Figure 4. In patients under 75 years of age, 72.5% (179/247) preferred once-monthly ibandronate. Among patients who were naïve to bisphosphonate treatment ($n = 247$), 72.6% preferred once-monthly ibandronate. Employment status did not seem to affect patient responses; the majority of patients preferred once-monthly ibandronate (71.6% of working patients and 71.1% of nonworking patients), irrespective of occupational status. Although the majority of patients ≥ 75 years old ($n = 29$) and the majority of lapsed daily bisphosphonate users ($n = 28$) preferred once-monthly ibandronate over once-weekly alendronate (60.7% and 54.5%, respectively), the once-monthly ibandronate preference did not reach statistical significance, most likely because of the small sample sizes.

Treatment preferences for once-monthly ibandronate and once-weekly alendronate as well as the reasons for preference (patients had the option of choosing multiple reasons) are shown in Table 1. The two most common reasons for choosing the monthly and weekly treatment regimens were (1) ease of following for a long time (169/197 and 70/79, respectively); and (2) a dosing schedule that fits better into the patient's lifestyle (152/197 and 59/79, respectively). More

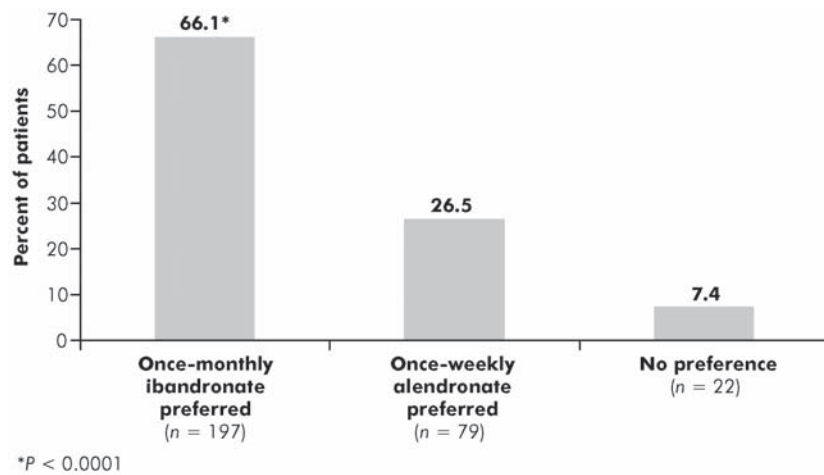


Figure 3. Summary of patient preferences for once-monthly ibandronate and once-weekly alendronate

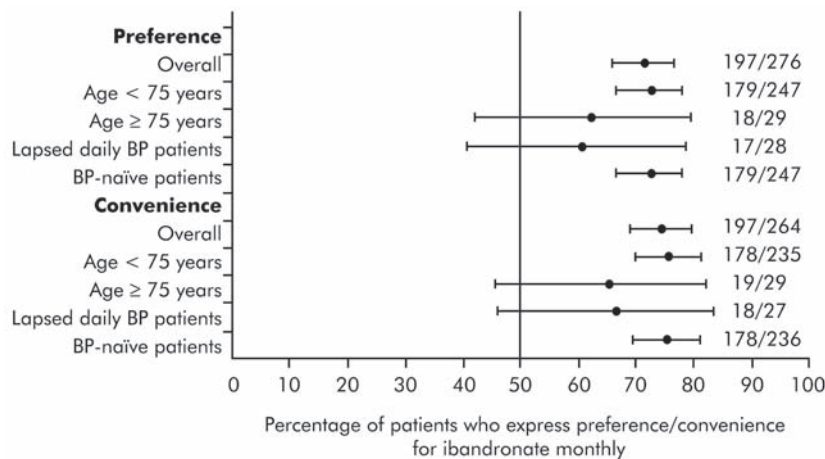


Figure 4. Percentage of patients who expressed preference/convenience for once-monthly ibandronate (excluding patients who did not express preference/convenience for one treatment). BP = bisphosphonate

patients who preferred once-monthly ibandronate chose 'it is easier to tolerate side effects overall' as a reason for their preference than those who preferred once-weekly alendronate (ibandronate, 47/197; and alendronate, 12/79); no statistical testing was performed on these data. Figure 5 depicts the reasons for preference given by all patients who expressed a preference for one treatment over another; 61% (169/276) of patients stated that they preferred once-monthly ibandronate because it would be easier to follow long-term, while 25% (70/276) of patients who preferred once-weekly alendronate chose the same reason.

Convenience

For women who expressed an opinion on convenience, 74.6% found once-monthly ibandronate to be more convenient and 25.4% found alendronate to be more convenient; the convenience rate for once-monthly ibandronate was statistically significant ($p < 0.0001$) (Figure 6A). Convenience opinions were not influenced by the treatment sequence (Gart-order-effect, $p =$

0.1570). Thirty-two patients (10.8%) were excluded from this analysis as they considered the two treatments to be equally convenient. Consistent results in favor of once-monthly ibandronate also were observed when the analysis was based on the full study population, including these 32 patients (ibandronate = 66.1%; alendronate = 22.6%), and again the convenience rate for once-monthly ibandronate was statistically significant ($p < 0.0001$) (Figure 6B).

Safety

The incidences of reported adverse events were generally comparable between patients receiving once-monthly ibandronate and once-weekly alendronate. Treatment-related adverse events were reported by 17.4% of patients while taking ibandronate and 17.8% of patients while taking alendronate. Treatment-related gastrointestinal (GI) adverse effects were reported by approximately 10% of patients while taking each drug. The incidence of upper GI events was 7.5% ($n = 24$) during ibandronate intake versus 9.4% ($n = 30$) during

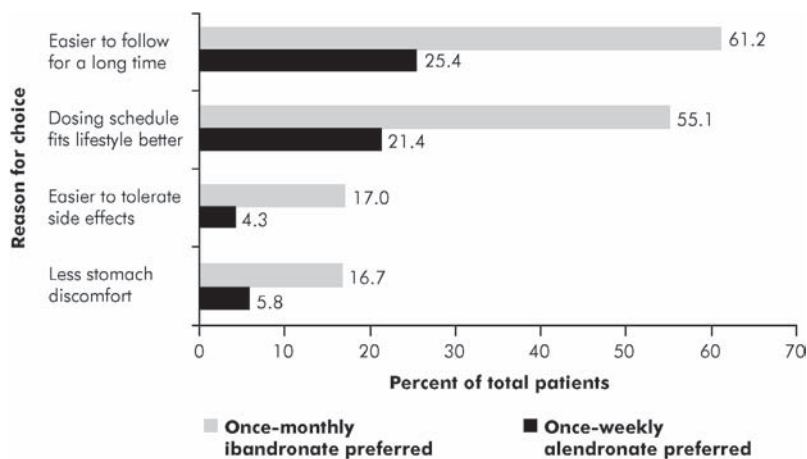


Figure 5. Patient preferences and reasons for preference. Excludes 22 patients who stated that they did not have a preference. Patients could provide more than one reason for choosing a particular regimen

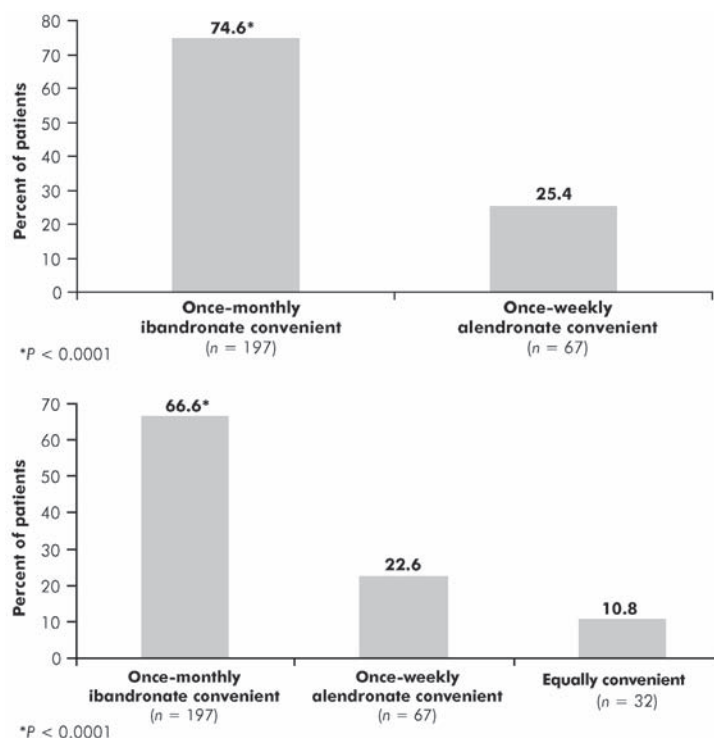


Figure 6. Summary of patient reports on convenience for once-monthly ibandronate and once-weekly alendronate. Top: analysis of patients who expressed an opinion on convenience for a treatment regimen. Bottom: analysis including patients who found both treatment regimens to be equally convenient

alendronate intake; 6.5% and 8.4% of the upper GI events, which occurred while taking ibandronate or alendronate, respectively, were considered to be treatment related. More patients receiving once-monthly ibandronate experienced diarrhea while more patients receiving once-weekly alendronate reported stomach discomfort and gastritis.

An interruption of scheduled medication occurred in six patients (1.9%) taking alendronate and in no patients taking ibandronate. The incidence of adverse events resulting in withdrawal from the study was 5.3% ($n = 17$) in patients receiving alendronate and 3.7% ($n = 12$)

in patients receiving ibandronate. Clinically relevant changes in laboratory parameters were not observed in any patient during the study.

Discussion

Ibandronate, which has recently been approved in the US and Europe for the prevention and treatment of PMO, is the first oral treatment for a chronic disease that can be administered as a once-monthly dose. This trial was the first clinical assessment of patient

preference and convenience opinions for once-monthly versus once-weekly bisphosphonate regimens. Preference, as examined in this study, represents an integrated assessment of the regimen, including the dosing frequency, the intake requirements, and the tolerability as experienced by the individual. A significantly greater proportion of patients preferred a once-monthly ibandronate regimen over a once-weekly alendronate regimen in this study. Preference for monthly dosing was observed to be independent of factors such as age and employment status.

Patient preferences for extended dosing intervals may ultimately contribute to greater rates of treatment adherence, including improved compliance with the dosing regimen as well as persistence with therapy. Various trials have shown better adherence rates for women receiving a once-weekly bisphosphonate regimen compared with a once-daily regimen, indicating that a correlation between patient preference and adherence is demonstrable for the daily and weekly bisphosphonates^{22,29,30}. However, these studies also showed that the percentage of women who continued once-weekly treatment declined to the range of 44–55% after approximately 12 months of therapy, indicating that while reducing the dosing frequency improves persistence, there is still significant room for improvement^{22,29,30}.

Adherence rates with bisphosphonate therapy have been shown to be even lower with prolonged treatment. In one claims database analysis, refill compliance and persistence rates dropped to 48% and 21%, respectively, in patients after 24 months of daily or weekly bisphosphonate therapy. Outcomes data from this population showed a 26% lower risk of fractures in patients who were refill compliant ($p < 0.0001$) and a 21% lower risk in patients who were persistent ($p < 0.0001$)³¹. These results suggest that facilitating adherence may in turn reduce the risk of fractures. Patient adherence to osteoporosis therapy – and bisphosphonates in particular – also has been demonstrated to reduce fracture rates significantly in other trials, underscoring the importance of optimizing adherence in this disease state^{32–34}. The recent Surgeon General's Report on bone health highlights this continuing need to improve patient adherence to osteoporosis medications². As patient preference has been identified to be a key determinant of adherence, involving patients in the decision-making process and offering them a choice of therapy may be an important step towards improving adherence rates, and ultimately, clinical outcomes.

While weekly bisphosphonate therapy has been preferred over daily therapy, in a recent survey involving approximately 400 women with osteoporosis receiving weekly bisphosphonate therapy, 63% stated that they would prefer a once-monthly treatment regimen, if one

were available²⁶. These findings are consistent with results from the present analysis of patient preferences based on experience with the once-monthly dose. The primary reasons that patients chose ibandronate in the present study were that the once-monthly regimen fit better into their lifestyle and was easier to follow over a long period of time; similar reasons were cited by patients who chose once-weekly alendronate. Tolerability also was an important factor for a number of patients. Less stomach discomfort was identified by 17% (46/276) of patients who preferred once-monthly ibandronate and by 6% (16/276) of patients who preferred once-weekly alendronate.

Limitations of this study include its open-label design – which was necessary given the study objectives. The randomization and cross-over design minimized this limitation. Another limitation is that the reasons for patient preference were limited to the four response options provided in the questionnaire. If patients preferred a treatment regimen for other reasons, this information was not captured in the present analysis. The trial was not designed to assess 'real-world' treatment adherence in patients who demonstrated a preference for either the monthly or weekly bisphosphonate regimen. However, it is important for prescribing clinicians to know the degree to which patient preferences may influence treatment adherence. While women with PMO in this study preferred once-monthly ibandronate to once-weekly alendronate, further studies on monthly bisphosphonate adherence will be required to determine if the patient preferences observed here will be associated with improved adherence.

Conclusions

In our study, significantly more women with PMO preferred once-monthly ibandronate therapy to once-weekly alendronate therapy, and found the once-monthly regimen to be more convenient. The most common reasons given for patient preference were ease of following a treatment regimen for a long time and the ability of a regimen to fit better into the patient's lifestyle. Given these results, physicians should consider offering once-monthly dosing to their postmenopausal patients when bisphosphonate therapy is deemed appropriate.

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