Effects of intermittent intravenous ibandronate injections on bone quality and micro-architecture in women with postmenopausal osteoporosis: The DIVA study

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A B S T R A C T
In the Dosing IntraVenous Administration (DIVA) study, IV ibandronate injections (15–30 s duration) provided significantly greater gains in bone mineral density than daily oral ibandronate (P < 0.001). Single transiliac bone biopsy was performed in a subgroup of women (n = 109/1395) from DIVA to assess the impact of ibandronate on newly formed bone and bone remodeling. Patients received ibandronate IV injections 2 mg every 2 months, 3 mg every 3 months or oral ibandronate 2.5 mg daily, plus oral or IV placebo, as appropriate to maintain blinding. Of the 1395 participants from the DIVA study, 122 were enrolled in the substudy. Qualitative histological analysis was performed on all biopsy cores and 89 cores were considered to be evaluable for quantitative histomorphometry. Following 2 years of ibandronate treatment, trabecular bone maintained its normal lamellar structure with no evidence of woven bone, marrow fibrosis, cellular toxicity, or other qualitative abnormalities. Primary mineralization of new bone remained normal, as indicated by the slightly lower osteoid thickness and osteoid volume, with normal mineral apposition rate compared to healthy, postmenopausal women. Mineralizing surface, osteoid surface, activation frequency and bone formation rate were decreased in all ibandronate-treated groups compared with values from healthy, postmenopausal women. Specifically, the bone formation rate (BFR/BV and BFR/BS) was approximately 5 times lower in the ibandronate-treated (3 mg) group than in healthy, postmenopausal women. Histomorphometric analysis of transiliac bone biopsies demonstrated normal micro-structure of newly formed bone with normal mineralization and reduced remodeling after oral or IV ibandronate.

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Introduction

Ibandronate is a potent, nitrogen-containing bisphosphonate that can be administered orally or intravenously with extended dosing intervals [1,2]. In the Dosing IntraVenous Administration (DIVA) study, intermittent IV ibandronate injections (15–30 s in duration) demonstrated superior efficacy (for bone mineral density [BMD] endpoints) compared with the daily oral ibandronate regimen with proven anti-fracture efficacy [3,4]. This study led to the licensing of IV ibandronate injections in the USA and Europe for the treatment of postmenopausal osteoporosis. The investigational IV regimens provided the highest annual cumulative exposure to ibandronate tested in women with postmenopausal osteoporosis (12 mg).

Robust efficacy was observed with oral ibandronate in the oral ibandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE) study; daily dosing reduced the relative risk of new vertebral fractures by 62% [5]. Although non-vertebral anti-fracture efficacy was not demonstrated in the overall population who were at low risk for such fractures (total hip BMD T-score: −1.7), a significant reduction in non-vertebral fracture risk was noted in patients with a BMD T-score of −3 (69%) [5]. The efficacy of oral ibandronate was reported alongside a favorable bone safety profile [6]. Following qualitative histology and quantitative histomorphometry analyses of bone biopsy samples, no impairment of bone mineralization was detected and no adverse effects on the structural quality of newly formed bone were observed. These clinical study findings are further supported by data from preclinical studies in various animal models of osteoporosis [2]. In rats, life-long administration of ibandronate, even when administered at doses higher than those used clinically (equivalent to 900 mg/day/60 kg patient), did not adversely affect bone structural quality or strength [7].

Demonstration that a new anti-osteoporosis treatment does not have a deleterious effect on bone mineralization and bone micro-structure is an important milestone. Determination of bone quality and micro-architecture is essential, as bone histomorphometry is a comprehensive and accurate method to evaluate bone quality. The effects of intermittent intravenous ibandronate injections on bone histomorphometry were evaluated in the DIVA study. This substudy provided an opportunity to assess the effects of intermittent intravenous ibandronate injections on bone histomorphometry.
architecture should form part of the overall analysis of safety. Bone histomorphometry is an established tool for evaluating quality of bone architecture and, when double labeling with tetracycline (a bone-seeking fluorochrome [8]) is used, it also allows assessment of the dynamic variables such as mineralization or bone formation rates. A subset of participants from DIVA was enrolled into a preplanned bone biopsy study that aimed to explore the bone safety profile of the oral and IV ibandronate regimens and confirm their effects on bone remodeling at the tissue level. The outcomes of the qualitative and quantitative histomorphometric analyses are reported herein.

Materials and methods

Study design

DIVA was a 2-year, randomized, double-blind, parallel-group, phase III, noninferiority study [3]. A bone biopsy substudy was conducted to evaluate the effect of IV ibandronate on bone safety, that is, the quality of newly formed bone and on the bone remodeling process. Only centers with the facilities to perform bone biopsies participated in this substudy.

Study population

Eligible participants, drawn from the overall population of the DIVA study [3], were postmenopausal women (aged 55–80 years, ≥5 years since menopause) with osteoporosis (lumbar spine [L2–L4] BMD T-score <−2.5) who provided written informed consent specifically for the bone biopsy substudy before randomization in the main clinical trial and again at year 2 prior to the start of any procedure in relation to the bone biopsy program.

In addition to the inclusion and exclusion criteria specified for the DIVA study [3], the following exclusion criteria were applied to all participants of the substudy: allergy or resistance to xylocaine or other locally administered anesthetic; pathological defects in hemostasis or anticoagulant treatment; local skin infection at the biopsy area; contraindications to tetracycline treatment; tetracycline use within the 12 months prior to screening and at any time during the study (excluding the use associated with the bone biopsy substudy) and previous horizontal transiliac bone biopsies of both ilia (right and left). Due to the double-blind nature of the main study, patients and investigators were not aware of the treatment or the results of any procedures, such as bone density assessment, at the time of biopsy.

Study medication

Participants were randomized to receive either 2 mg every 2 months (q2mo) IV ibandronate injections (plus daily oral placebo), 3 mg every 3 months (q3mo) IV ibandronate injections (plus daily oral placebo) or 2.5 mg daily oral ibandronate (plus q2mo or q3mo IV placebo injections). All participants received daily calcium (500 mg) and vitamin D (400 IU) supplements.

Biopsy procedure

Single transiliac bone biopsies were taken after 22 months (q3mo arms) or 23 months (q2mo arms) of oral or IV treatment and within a few days of the next planned IV dose. Prior to biopsy, double tetracycline labeling, with oral tetracycline HCl (250 mg four times daily), was performed according to the following schedule: 3 days of tetracycline (Label 1), 14 days without tetracycline, 3 days of tetracycline (Label 2); biopsies were performed 5–14 days after the end of Label 2. All biopsy samples were analyzed centrally (Creighton University Osteoporosis Research Center, Creighton University, Omaha, Nebraska, USA).

Analyses

All analyses of bone histomorphometry were prespecified and were performed blind to treatment allocation. Embedding, sectioning, staining and reading the specimens were performed according to well-established procedures [9]. All biopsies were obtained with a trephine of 7.5 mm in diameter. Each biopsy specimen was sectioned at two levels that were 300 μm apart and contained within the middle of the specimen. At each of these levels, one section was stained with Goldner’s stain, another with Toluidine blue, and one section was left unstained (all sections were 5 μm in thickness). If the sum of the areas available for histomorphometry (i.e., the sum of the areas from the two Goldner’s sections, each >300 μm apart) was less than 20 mm², then no histomorphometric static or dynamic variables were reported. The microscopist stayed at least one trabecular width (∼130 μm) away from the cortico-endosteal surface to avoid including this surface in the histomorphometric measurements. This was done to avoid confounding the values for trabecular histomorphometry with measurements that included the cortico-endosteal surface, a surface that behaves differently from the trabecular bone surface. The area less than one trabecular width (∼130 μm) from the cortico-endosteal surface was not included in the 20 mm² section required for histomorphometric analysis. The combined mean total area examined for each pair of sections was 46.7 ± 10.4 mm² (standard deviation [SD]), with values ranging from 23.9 mm² to 76.8 mm². None were less than 23.9 mm². Areas at the edges of the sections that contained ‘bone dust’, i.e., small fractured particles caused by the teeth of the trephine, were also avoided. The area on which measurements were performed was required to be free from artifacts. Histomorphometry was reported for specimens that had only one cortex if there was at least 20 mm² of total trabecular area free from artifacts. For extended label search, the above sections were reviewed for the presence of tetracycline labels in the endosteal and cortical regions. If no labels were found on existing sections, four additional sections were cut some 300 μm further into the specimen. If no labels were found in the first set of additional sections, another set was cut some 300 μm further into the specimen. The tetracycline label findings were then recorded (single or double label) on the first or second set of recut sections. Only the presence or absence of label was recorded for the sections from the extended label search. Extended label search was not performed in eight biopsies where no double label was found on the trabecular surfaces in the standard sections. However, all eight exhibited either single label on trabecular surfaces, or double label in the cortices in the standard sections. No label was found in the standard sectioning protocol in four biopsies where extended label searches were performed. Static data were reported for three of these four biopsies. The fourth one was among the 20 specimens that were not evaluable for histomorphometry. The remainder on the non-evaluable specimens contained label in the standard sections. Thus, there were 12 biopsies where label problems occurred. For 11 of these 12 biopsies, all the dynamic remodeling data were treated as zero values except for MAR, MLT and A1AR, which were treated as missing values. However, all 89 did contribute data from the standard 2-level sectioning protocol for the analysis of static variables.

Qualitative histological analysis

A qualitative histological analysis was performed to detect the presence of woven bone, marrow fibrosis, mineralization defects, cellular toxicity and other abnormalities. The presence or absence of woven bone was determined on the basis of qualitative evaluation of the biopsy specimens, both stained and unstained. Cellular toxicity was assessed qualitatively by viewing the appearance of the bone cells, that is, osteoclasts, osteoblasts, lining cells and osteocytes.
Quantitative histomorphometric analyses

Variables expressing bone mineralization

Osteoid thickness (O.Th) is a measure of the average thickness of newly formed, osteoblast-derived, non-mineralized osteoid matrix and, with the mineral apposition rate (MAR; the linear velocity of mineralization of new osteoid as determined by the distance between the two tetracycline labels, divided by the time interval between tetracycline labels), is used to calculate the mineralization lag time (MLT; MLT = O.Th/Aj.AR [Aj.AR = adjusted apposition rate], the mean interval between the deposition of osteoid and its subsequent mineralization), a sensitive measure of mineralization defects of newly formed bone. Other parameters assessed were osteoid volume (OV/BV; the fraction of bone volume that is non-mineralized osteoid) and Aj.AR (representing the bone formation rate averaged over the entire osteoid surface, adjusted for the osteoid surface being larger than the mineralizing surface). It was expected, following oral and IV ibandronate, that treatment-induced reduction in bone turnover would result in slight changes in these variables of bone mineralization.

Variables expressing bone remodeling

The following histomorphometric variables were calculated to assess the level of bone remodeling: mineralizing surface (MS/BS; the fraction of trabecular surface undergoing bone formation, as judged by double plus one half of the single label surface), activation frequency (Ac.f; the probability that a new cycle of remodeling will be initiated at any point on the trabecular surface), osteoid surface (OS/BS; the percentage of cancellous surface with unmineralized osteoid, with and without osteoblasts), bone formation rate (BFR/BS and BFR/BV; estimates of the annual volume of new trabecular bone formed per unit trabecular surface and per unit trabecular bone volume, respectively) and eroded surface (ES/BS; a static feature representing the percent of trabecular surface occupied by Howship’s lacunae where osteoclasts have eroded or are eroding the sites of new basic structure units). Ac.f correlates well with bone remodeling under most circumstances. However, bisphosphonate therapy interferes with osteoclast work, and not with osteoclast differentiation. Since there is no marker of osteoclast differentiation, nor of the amount of bone removed, Ac.f must be interpreted in the context of the histomorphometric values expressing bone formation.

Variables expressing bone micro-architecture

Trabecular thickness (Tb.Th; the mean width of trabecular profiles, a structural variable that is maintained in patients with osteoporosis until the reduction in trabecular bone is extreme), trabecular number (Tb.N) and trabecular separation (Tb.Sp; the mean intertrabecular distance) are calculated from the cancellous bone area and volume and length of the bone interface.

Variables expressing bone structure

Wall thickness of trabecular packets (W.Th; the mean width of packets) and bone volume (BV/TV; derived from the percentage area bone [mineralized and osteoid] occupying the marrow space) were also assessed.

Statistical methods

No formal sample size calculations were performed for the bone biopsy substudy. Sample size was based on operational considerations and, in agreement with the Food and Drug Administration, 96 evaluable bone biopsies were considered to be sufficient. This substudy was not powered to test a null hypothesis, and analysis of all bone biopsy safety parameters was based on exploratory methods using descriptive statistics. Mean and median values (plus 90% confidence intervals [CIs] for the medians and median differences were calculated for all quantifiable parameters. Data from the two IV arms (with either q2mo or q3mo placebo injections) were pooled for analysis. Although post hoc, exploratory significance tests have been carried out comparing the oral and IV regimens, the study was not powered for these individual or multiple comparisons. The Kruskal–Wallis test, a non-parametric method of testing the hypothesis that two or more populations have the same continuous distribution versus the alternative that measurements tend to be higher in one of the populations, was used to complete the post hoc analysis. It is recommended that they are interpreted with caution and with reference to the 90% CIs. Formal tests were not performed to check normal distribution as a result of the type of data, limited sample size and there being some variables with skewness (in terms of mean and medians differing). As expected, the data were not normally distributed.

With the aim of providing interesting additional information, where appropriate, values were also compared with normal (reference) data from 34 healthy postmenopausal women (aged 45–75 years, average 13 years since menopause) [9]. Although the same procedures for quantitative and qualitative histomorphometry remain in place, it would be noted that the data for healthy postmenopausal women were obtained approximately 20 years previously.

Results

Patient disposition and characteristics

Two hundred fifty-four patients who consented to bone biopsy at the start of the study were reassessed for eligibility and asked to confirm consent at month 22 or month 23, as appropriate. Of the 254 patients who consented to bone biopsy at the start of the study, 132 patients withdrew their consent at year 2. A total of 122 participants, from the 1395 participants randomized in the DIVA study, were enrolled in the substudy and a single transiliac bone biopsy was obtained from 109 participants (1 lost biopsy, 2 unsuccessful biopsies, 3 biopsies not performed, 6 withdrew consent/did not re-consent, 1 withdrawal due to a serious adverse event).

Qualitative histological analysis was performed on all biopsy cores irrespective of whether they were adequate for quantitative histomorphometric analyses. From the collected samples, 89 were unbroken and considered to be evaluable (intact and/or at least one cortex) for quantitative histomorphometric analysis: 32 in the daily arm, 27 in the q2mo arm and 30 in the q3mo arm. Twenty biopsy specimens were not evaluable (7 in the daily arm, 9 in the q2mo arm and 4 in the q3mo arm) due to an inadequate biopsy sample (15 were fragmented or contained insufficient tissue and 5 were broken or cracked).

Of the evaluable samples (n = 89), 11 did not exhibit double label on the trabecular surfaces in the standard, 2-level sectioning protocol. Four of these samples exhibited single label on trabecular surfaces and double label in the cortices. Four samples exhibited single and double label in the cortices but no single or double label on the trabecular surfaces. Three samples underwent extended label searches (along with one specimen in the non-evaluable group where the label was found in the extended label search). Of this group, one sample exhibited single trabecular label, one sample had single cortical label, and two were found to have no label. This is consistent with previous experience that about 3–4% of biopsy specimens from untreated osteoporosis patients do not exhibit label in trabecular bone or cortices in the standard 2-level sectioning protocol [10]. Due to an absence of double label in trabecular bone among the standard sections in 11 samples, 78/89 samples were considered evaluable for a complete set of both static and dynamic histomorphometry measurements. Of the 12 samples without double label, those that exhibited single label provide evidence that the label schedule was followed, but remodeling was reduced to the extent that remodeling dynamics could not be calculated. In the two cases without double or single labels on trabecular surfaces or in the cortices the extended
results for IV ibandronate compared with daily ibandronate and the mineralization of newly formed bone was detected. The detailed Bone mineralization analyses presented are based on median values. Quantitative histomorphometric analyses abnormally large numbers of nuclei. cellular toxicity or indicators of osteomalacia, such as excessive signs of woven bone. Newly formed bone was identified as adjacent to osteoid in a formation site (in the absence of a mineralizing defect) or at the site of double or single label. No marrow fibrosis, signs of cellular toxicity or indicators of osteomalacia, such as excessive osteoid, were observed. In addition, there were no osteoclasts with abnormally large numbers of nuclei. Quantitative histological analysis

The qualitative histological analysis did not show abnormal findings. In all patients in the IV and oral ibandronate treatment groups, newly formed bone retained its lamellar structure, without signs of woven bone. Newly formed bone was identified as adjacent to osteoid in a formation site (in the absence of a mineralizing defect) or at the site of double or single label. No marrow fibrosis, signs of cellular toxicity or indicators of osteomalacia, such as excessive osteoid, were observed. In addition, there were no osteoclasts with abnormally large numbers of nuclei.

Quantitative histomorphometric analyses

As expected, the data were not normally distributed therefore analyses presented are based on median values. Bone mineralization

In all ibandronate treatment arms, no impairment of the mineralization of newly formed bone was detected. The detailed results for IV ibandronate compared with daily ibandronate and the healthy postmenopausal reference group are presented in Table 2. As anticipated, median O.Th values were generally comparable across the IV and oral ibandronate arms with no statistically significant difference found and were lower than the healthy postmenopausal reference value; this is primarily due to the observed reduction in Ac.f on treatment. A similar outcome was seen for OV/BV and OS/BS. The median values for MAR, Aj.AR and MLT were generally similar across all treatment arms with no statistically significant differences found. As expected, MAR was comparable to the healthy postmenopausal reference value and although normal ranges have not been calculated for Aj.AR these levels are commonly seen in normal and osteoporotic subjects. The difference in MLT between the ibandronate groups and the reference value was not unexpected as calculation of this variable includes the value for O.Th.

Bone remodeling

The variables expressing bone remodeling, presented in Table 3, were generally comparable in all treatment arms, which was expected. Exploratory testing indicates that median Ac.f values were significantly lower in the IV treatment groups compared with oral ibandronate and were also lower than reference values observed in untreated osteoporotic (0.42/year [11]) and healthy postmenopausal women (Table 3). Importantly, median Ac.f values were similar to the reference value seen in healthy premenopausal women (0.13/year, 95% CI 0.02–0.63) [11]. Median values for MS/BS and OS/BS, were broadly similar across the active treatment groups, although exploratory testing indicates that MS/BS was significantly lower in the 2 mg IV group compared with daily ibandronate, and they were lower than the healthy postmenopausal reference value, as anticipated. Results for MS/BS were not markedly different to those seen in healthy premenopausal women (4.02%, 95% CI 0.61–8.42, data on file). The median values for BFR/BV and BFR/BS were comparable in the 3 mg IV group and lower in the 2 mg IV group compared with daily oral ibandronate. BFR/BV and BFR/BS are directly affected by changes in Ac.f, therefore, given that there was no evidence of impairment of mineralization in newly formed bone in any of the ibandronate-treated patients, the decreases in the ibandronate-treated groups compared with the reference value were expected. The median ES/BS values were slightly lower than those of the reference values, although the individual values generally overlapped the normal range.

Bone micro-architecture

Bone micro-architecture was normal in all treatment arms; the results are presented in Table 4. Compared with healthy postmenopausal reference values and due to the osteoporotic status of the study subjects, Tb.N was lower in the ibandronate treatment groups. Linked to the lower Tb.N values, Tb.Sp was higher with active treatment than the reference values. Median values for Tb.Th were 7.8–16.4% greater with IV ibandronate compared to the healthy postmenopausal reference value, however, all values for IV ibandronate were within the reference range. Median W.Th and BV/TV values were similar between groups and the reference values. No statistically significant differences between the oral and IV ibandronate groups have been
reported for the micro-architectural variables. The micro-architecture variables presented in Table 4 have relatively large confidence limits and BV/TV is intrinsically quite variable, thus it is difficult to detect small differences between groups. In addition, as medians have been used for expressions of central tendency due to non-normal distributions, small, but real differences between the groups may be further obscured.

Overall tolerability and safety

The incidence of adverse events has not been reported specifically for this subgroup. In the overall study population the safety profile of IV ibandronate was similar to that reported with oral ibandronate [3].

Discussion

The DIVA bone biopsy study provides important new information regarding the bone safety profile of ibandronate when administered by IV injection with an annual cumulative exposure of 12 mg, which is two times greater than the annual cumulative exposure for 2.5 mg daily ibandronate (~5.5 mg). Independent of the ibandronate dose or route of administration, lamellar structure was retained, with no signs of woven bone, marrow fibrosis, cellular toxicity or indicators of osteomalacia detected in newly formed bone. With regard to the latter, we saw a small reduction in O.Th and OV/BV, the opposite of that seen in osteomalacia. We hypothesize that compared with healthy postmenopausal women, an effective treatment with a remodeling suppressor would result in a lower O.Th and OV/BV, since the average age of the osteons is greater, and the average length of time for mineralization is greater. The quantitative analyses of bone histomorphometry found no impairment of mineralization of newly formed bone following treatment with ibandronate. These results are consistent with previous histomorphometric analyses of daily and intermittent oral ibandronate [6]. Mineralizing surface, O.S/B, Ac.f and bone formation rates were decreased in all three groups of ibandronate-treated patients in comparison with normal, age-matched reference values, to a range similar to that seen in healthy premenopausal women. Values for bone safety and micro-architecture parameters were normal and generally comparable across the oral and IV ibandronate arms [11]. The ibandronate results are consistent with those expected for an efficacious biphosphonate and are within the range of those seen with daily oral alendronate (10 mg) [12] and risedronate (5 mg) [13].

The bone biopsies from DIVA were analyzed in a manner similar to those from a previous bone biopsy study with oral ibandronate (BONE) [6]; biopsies underwent tetracycline labeling and the number of biopsies evaluable for quantitative analyses (dynamic and static parameters) were comparable (78/89 and 100/110 for DIVA and BONE, respectively) [6]. A post hoc statistical analysis was completed to compare the changes in histomorphometric variables between the daily oral and quarterly IV injection regimens. However, the results of this analysis should be treated with caution due to the potential for false positive results due to the multiple significance tests and lack of power calculation. It is recommended that the P values are considered in conjunction with the 90% CIs, as these provide a measure of the variability. More importantly, the findings from the DIVA bone biopsy substudy were consistent with those reported for the BONE study, which compared daily and intermittent oral ibandronate with placebo [6], and those observed in relevant reference populations [9,11].

As with the IV regimens in DIVA, 150 mg monthly oral ibandronate provided at least equivalent efficacy and similar safety to daily (2.5 mg) oral ibandronate in women with postmenopausal osteoporosis in MOBILE (Monthly Oral iBandronate In LadiEs study) [14,15]. This regimen has an annual cumulative exposure similar to the IV

<table>
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<th>Table 3</th>
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<tr>
<td>Median (90% CI) and P values (90% CI for the difference in the medians) for comparison between IV regimens and oral ibandronate for parameters of bone remodeling in DIVA plus normal reference values (healthy postmenopausal women; median [normal range]).</td>
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</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2.5 mg daily oral ibandronate (n = 32)</th>
<th>2 mg q2mo IV ibandronate (n = 27)</th>
<th>3 mg q3mo IV ibandronate (n = 30)</th>
<th>Reference values (n = 34)</th>
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<tbody>
<tr>
<td>Ac.f (no./year)</td>
<td>0.11 (0.07, 0.20)</td>
<td>0.04 (0.02, 0.09)</td>
<td>0.05 (0.04, 0.13)</td>
<td>0.37 (0.06, 0.94)*</td>
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<tr>
<td>MS/BS (%)</td>
<td>1.64 (0.82, 2.94)</td>
<td>0.61 (0.39, 1.29)</td>
<td>0.87 (0.60, 1.89)</td>
<td>6.10 (1.00–13.50)</td>
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<td>OS/BS (%)</td>
<td>5.69 (4.93, 8.22)</td>
<td>5.12 (2.48, 7.38)</td>
<td>4.36 (2.55, 6.71)</td>
<td>12.80 (7.00–25.00)</td>
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<td>BFR/BV (mm²/mm²/year)</td>
<td>0.04 (0.03, 0.08)</td>
<td>0.01 (0.01, 0.03)</td>
<td>0.03 (0.02, 0.06)</td>
<td>0.19 (0.02–0.48)</td>
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<td>BFR/BS (%)</td>
<td>0.004 (0.0021, 0.0063)</td>
<td>0.001 (0.0007, 0.0027)</td>
<td>0.002 (0.0014, 0.0039)</td>
<td>0.011 (0.001–0.025)</td>
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<td>ES/BS (%)</td>
<td>1.62 (1.32, 1.88)</td>
<td>1.40 (1.07, 2.16)</td>
<td>1.29 (1.04, 1.95)</td>
<td>3.4 (1.75–7.0)</td>
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<th>Parameter</th>
<th>25 mg daily oral ibandronate (n = 32)</th>
<th>2 mg q2mo IV ibandronate (n = 27)</th>
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<tr>
<td>Tb.N (n/mm)</td>
<td>1.34 (1.26, 1.42)</td>
<td>1.30 (1.15, 1.48)</td>
<td>1.30 (1.28, 1.42)</td>
<td>1.67 (1.20–2.00)</td>
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<tr>
<td>Tb.Sp (µm)</td>
<td>732 (688, 792)</td>
<td>748 (695, 861)</td>
<td>587 (480–850)</td>
<td></td>
</tr>
<tr>
<td>Tb.Th (µm)</td>
<td>146 (134, 163)</td>
<td>149 (131, 180)</td>
<td>138 (128, 155)</td>
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<tr>
<td>W.Th (µm)</td>
<td>32.00 (30, 33)</td>
<td>31.50 (31, 33)</td>
<td>31.00 (25–38)</td>
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<td>BV/TV (%)</td>
<td>19.7 (16.2, 22.7)</td>
<td>20.2 (18.3, 23.3)</td>
<td>18.4 (16.7, 20.7)</td>
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* Median (95% CI) [11].
  ** BFR/BV = (365.25 * MAR/MS/BS/IV/T) / 1000 * BV/TV; to change to %/year multiply by 100.
  † BFR/BS = (MAR/MS/BS * 365.25) / 100 mm²/mm²/year.

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<td>32.00 (30, 33)</td>
<td>31.50 (31, 33)</td>
<td>32.80 (32, 34)</td>
<td>18.4 (16.7, 20.7)</td>
</tr>
<tr>
<td>BV/TV (%)</td>
<td>19.7 (16.2, 22.7)</td>
<td>20.2 (18.3, 23.3)</td>
<td>18.4 (16.7, 20.7)</td>
<td>20.8 (14–30)</td>
</tr>
</tbody>
</table>
ibandronate regimens in DIVA (annual cumulative exposure ~12 mg) [3,15] and, therefore, bone would be exposed to similar levels of ibandronate for these oral and IV regimens. It is possible, therefore, that the positive histomorphometric and bone safety profiles observed with intermittent IV ibandronate injection may also reflect the effects of 150 mg monthly ibandronate.

The number of specimens not exhibiting trabecular double fluorochrome label (in the standard sectioning protocol) during treatment matches the number (4 of 89) found in a study of untreated osteoporosis patients [10]. Thus, while fluorochrome label was absent in three of the 89 biopsy specimens, overall, these findings indicate that ibandronate, when administered for up to 2 years with extended between-dose intervals and an annual cumulative exposure of up to 12 mg, has a favorable bone safety profile. Reflecting the antiresorptive mechanism of action and in combination with the positive efficacy outcomes of the DIVA study, these findings further support the use of ibandronate quarterly IV injections in postmenopausal osteoporosis, particularly for those patients in whom oral dosing is unsuitable.

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References


