Intermittent intravenous ibandronate injections have a similar bone safety profile to daily oral dosing

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SUMMARY

- In the Dosing IntraVenous Administration (DIVA) study, 2mg every 2 months (q2mo) and 3mg every 3 months (q3mo) intravenous (i.v.) ibandronate (Bonviva®) injections produced superior efficacy to 2.5mg daily oral ibandronate (for bone mineral density [BMD] endpoints) in women with postmenopausal osteoporosis; in an earlier study, this oral regimen had no adverse effects on the quality of newly formed bone.
- Qualitative histological and quantitative histomorphometric analyses were performed in DIVA after 22 or 23 months to assess the impact of the oral and i.v. regimens on the quality of newly formed bone and the bone remodelling process in a subset of patients (n=89) who underwent single bone biopsy.
- In all patients, newly formed bone was of normal lamellar structure, without signs of woven bone, marrow fibrosis or cellular toxicity; no evidence of osteomalacia, such as an excessive amount of osteoid or abnormal mineral apposition rate (MAR), was observed.
- Values for activation frequency (Ac.f) and mineralising surface (MS) were broadly similar in the i.v. and oral treatment arms and lower than healthy postmenopausal reference values; in both cases, values were not markedly different from those seen in healthy premenopausal women and an earlier study of daily oral ibandronate.
- In conclusion, 2mg q2mo and 3mg q3mo i.v. ibandronate injections have similar bone safety profiles to daily oral ibandronate in women with postmenopausal osteoporosis; no adverse effects on bone mineralisation were detected and the rate of bone remodelling was reduced to healthy premenopausal levels. These findings are noteworthy, since the annual cumulative exposure (ACE) to ibandronate provided by the i.v. regimens (12mg) is the highest tested so far in women with postmenopausal osteoporosis.

INTRODUCTION

- Histomorphometry is a powerful tool for evaluating the effects of therapeutics on bone quality and the bone remodelling process at the tissue level.
- In the oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE) of daily (2.5mg) and intermittent (20mg every other day for 12 doses every 3 months; dosing interval >2 months) oral ibandronate, a nitrogen-containing bisphosphonate for postmenopausal osteoporosis, analyses of single bone biopsy samples taken at 3 years demonstrated that newly formed bone was of normal quality and structure; moreover, no adverse effects on mineralisation were detected.[1,2]
- The subsequent DIVA study, a randomised, double-blind, double-dummy, phase III, non-inferiority study, demonstrated the superior efficacy of 2mg q2mo and 3mg q3mo i.v. ibandronate injections versus the 2.5mg daily oral ibandronate regimen; qualitative histological and quantitative histomorphometric analyses were also performed at 22 or 23 months to establish the bone safety profile of the investigational regimens and provide further insights into their impact on the bone remodelling process.[3,4]
- The outcome of this analysis, which provides safety information on the highest ACE to ibandronate examined to date (12mg), is reported herein.

METHODS

Bone biopsy study design and patient population

- All participants were postmenopausal women (aged 55–80 years, ≥5 years since menopause [YSM]) with osteoporosis (lumbar spine [L2–L4] BMD T-score <–2.5) who received 2 years' treatment with daily calcium (500mg) and vitamin D (400IU), plus either 2mg q2mo i.v. ibandronate injections (plus daily oral placebo), 3mg q3mo i.v. ibandronate injections (plus daily oral placebo) or 2.5mg daily oral ibandronate (plus q2mo or q3mo i.v. placebo injections); written informed consent was provided by all those entering the biopsy study.
- Single transiliac bone biopsies were taken after 22 months (q3mo arms) or 23 months (q2mo arms) of oral or i.v. treatment; prior to biopsy, double tetracycline labelling was performed in 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 analysed centrally (Creighton University Osteoporosis Research Center, Creighton University, Omaha, Nebraska, USA).

Analyses

- A qualitative histological analysis was performed to detect the presence of woven bone, marrow fibrosis, mineralisation defects and cellular toxicity.
- Quantitative histomorphometric analyses included both static (e.g. osteoid thickness [O.Th], osteoid volume [OV/BV], trabecular thickness [Tb.Th], trabecular number [Tb.N] and trabecular separation [Tb.Sp]) and dynamic (e.g. MAR, Ac.F, MS/BS and bone formation rate [BFR/BV]) parameters.
- For between-group comparisons, median values and 90% CIs were calculated for all quantitative parameters; data were also compared with normal (reference) data from a patient population consisting of 34 healthy postmenopausal women (aged 45–75 years, ≥1 YSM).[5,6]

RESULTS

Study population and patient characteristics

- A total of 109 participants underwent a single transiliac bone biopsy.
- Qualitative histological analysis was performed on all biopsy cores.
- Quantitative histomorphometric parameters were evaluable in 89 samples: 32 in the daily arm, 27 in the q2mo arm and 30 in the q3mo arm; static parameters were evaluable in all samples and dynamic parameters in 77 samples.
- Baseline characteristics of the participants providing evaluable samples were well balanced across the treatment arms (**Table 1**).

Table 1. Baseline patient characteristics of participants providing evaluable samples (mean, SD).

	2.5mg daily oral IBN (n=32)	2mg q2mo i.v. IBN (n=27)	3mg q3mo i.v. IBN (n=30)
Age (years)	62.9 (6.70)	65.3 (6.71)	63.4 (6.79)
Weight (kg)	64.5 (9.55)	68.3 (11.44)	65.7 (10.63)
Height (cm)	159.4 (6.41)	157.5 (4.92)	161.0 (6.68)
YSM (years)	15.8 (9.43)	18.7 (10.04)	17.1 (7.48)
Fracture history (n, %)			
Yes	12 (37.5)	13 (50.0)	15 (50.0)
No	20 (62.5)	13 (50.0)	15 (50.0)

Qualitative histological analysis

- In the i.v. and oral treatment groups, newly formed bone retained its lamellar structure, without signs of woven bone.
- No marrow fibrosis, signs of cellular toxicity or indicators of osteomalacia, such as excessive osteoid, were found.

Quantitative histomorphometric analysis

Bone mineralisation

- In all treatment arms, no impairment of mineralisation of newly formed bone was detected with active treatment
  - median O.Th values were generally comparable across the i.v. and oral treatment arms and lower than the healthy postmenopausal reference value, as anticipated (**Table 2**); a similar outcome was observed for OV/BV (**Table 2**)
  - median MAR values were comparable in all treatment arms and also comparable to the healthy postmenopausal reference value, as expected (**Table 2**).

Bone turnover

- As expected, parameters of bone turnover were comparable in all treatment arms
  - median Ac.F values were generally similar in all active treatment groups (**Table 2**), yet lower than reference values observed in untreated osteoporotic (0.42/year)[6] and healthy (**Table 2**) postmenopausal women; importantly, values were similar to the reference value seen in healthy premenopausal women (0.13/year)[6]
  - median values for MS/BS were broadly similar across the active treatment groups (**Table 2**), but were markedly lower than the healthy postmenopausal reference value, as anticipated (**Table 2**); again, results were not markedly different to that seen in healthy premenopausal women[6]
  - as expected, median values for BFR/BV tended to be lower than the healthy premenopausal reference value (**Table 2**).

Bone micro-architecture

- Normal bone micro-architecture was observed in all treatment arms
  - median values for Tb.Th were comparable to the healthy postmenopausal reference value (**Table 2**)
  - compared with healthy postmenopausal reference values, Tb.N was lower and Th.Sp higher in the active treatment groups, as anticipated (**Table 2**).

Table 2. Summary of key histomorphometric parameters (median, 90% CI) in DIVA plus normal reference values (healthy postmenopausal women).

	2.5mg daily oral IBN (n=32)	2mg q2mo i.v. IBN (n=27)	3mg q3mo i.v. IBN (n=30)	Reference values (n=34)[5,6]
Mineralisation				
O.Th (μm)	5.00 (4.80, 5.70)	4.70 (4.40, 5.20)	5.05 (4.70, 5.90)	9.58
OV/BV (%)	0.61 (0.40, 0.91)	0.40 (0.22, 0.70)	0.45 (0.28, 0.59)	1.78
MAR (μm/day)	0.63 (0.55, 0.64)	0.56 (0.49, 0.61)	0.60 (0.54, 0.66)	0.53
Bone turnover				
Ac.f (no./year)	0.13 (0.08, 0.23)	0.06 (0.03, 0.11)	0.06 (0.05, 0.14)	0.37
MS/BS (%)	1.64 (0.82, 2.94)	0.61 (0.39, 1.29)	0.87 (0.60, 1.89)	6.1
BFR/BV (mm^2/mm^2/year)	0.05 (0.04, 0.10)	0.02 (0.01, 0.04)	0.04 (0.02, 0.08)	0.19
Trabecular bone micro-architecture and structure				
Tb.Th (μm)	146.5 (134, 163)	149.0 (131, 180)	138.0 (128, 155)	128
Tb.N (%)	1.34 (1.26, 1.42)	1.30 (1.15, 1.48)	1.30 (1.28, 1.42)	1.67
Tb.Sp (μm)	732.5 (688.0, 792.0)	748.0 (695.0, 861.0)	753.5 (689.0, 771.0)	587

CONCLUSIONS

- In postmenopausal women with osteoporosis, 2mg q2mo and 3mg q3mo i.v. ibandronate injections (providing an ACE of 12mg) have a bone safety profile that is generally comparable to the daily oral regimen; no adverse effects on the quality of newly formed bone were detected and no impairment of bone mineralisation was observed.
- This finding is noteworthy, since the ACE to ibandronate provided by the i.v. regimens is the highest tested to date in osteoporotic women.

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