Oral ibandronate is as active as intravenous zoledronic acid for reducing bone turnover markers in women with breast cancer and bone metastases

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Background: Phase III study comparing the effect of oral ibandronate and intravenous zoledronic acid on bone markers.

Patients and methods: Breast cancer patients with bone metastases received ibandronate 50 mg/day (n = 137) or zoledronic acid 4 mg every 4 weeks (n = 138) for 12 weeks. The primary end point was mean percentage change in serum levels of cross-linked C-terminal telopeptide of type I collagen (S-CTX) at week 12. Urinary CTX (U-CTX), bone alkaline phosphatase (ALP), amino-terminal procollagen propeptide of type I collagen (PINP) and osteocalcin (OC) were also measured and bone pain and safety assessed.

Results: Both bisphosphonates significantly reduced S-CTX (mean ibandronate 76% ± 29 (SD) versus mean zoledronic acid 73% ± 47; P < 0.001 for both versus baseline) and U-CTX (ibandronate 78% ± 30 versus zoledronic acid 86% ± 17; P < 0.001). The difference in S-CTX between treatments was 0.6% (confidence interval −1.7% to 3.0%), which was within the prespecified noninferiority margin. Bone ALP, PINP and OC decreased by 26%–47% compared with baseline with both bisphosphonates. Compared with zoledronic acid, ibandronate patients reported fewer adverse events overall (65.0% versus 75.9%), and on days 1–3 (8.0% versus 47.5%), including less pyrexia (overall incidence 0% versus 16.8%) and bone pain (5.8% versus 12.4%).

Conclusions: Oral ibandronate was well tolerated and statistically noninferior to zoledronic acid for percentage change in the bone resorption marker, S-CTX.

Key words: bisphosphonates, bone markers, bone metastases, ibandronate, zoledronic acid

introduction

Bisphosphonates such as clodronate, ibandronate, pamidronate and zoledronic acid are the standard of care for patients with metastatic bone disease [1, 2] with proven ability to reduce the risk of skeletal-related events [3–8]. Bisphosphonates also play an important role in relieving metastatic bone pain [5, 9–11]. Bisphosphonates directly inhibit osteoclast-mediated bone resorption. They are selectively taken up by the bone, where they inhibit osteoclast maturation and function, leading to osteoclast apoptosis [12, 13].

Biochemical markers of bone resorption show potential in the initial evaluation of bone metastases, as surrogates of disease progression, as fracture predictors and as prognostic factors of survival [14–17]. In addition, serum levels of biochemical markers of bone cell activity are increasingly recognized as useful determinants for assessing the clinical response to antineoplastic and antiresorptive therapy in metastatic bone disease [15, 18]. Suppression of bone turnover markers with bisphosphonate therapy has been correlated with a global reduction in skeletal-related events, [19–22] and there is limited evidence of a similar relationship between bone resorption markers and pain following treatment with bisphosphonates [23, 24].

This phase III, open study is the first to compare directly the effect of treatment with oral ibandronate and intravenous (i.v.) zoledronic acid on markers of bone resorption and formation. The respective safety profiles of the two bisphosphonates are also reported.

patients and methods

study population

The study population comprised female patients with histologically confirmed breast cancer and at least one osteolytic or mixed bone lesion, confirmed by radiological assessment. Eligibility criteria included age 18 years or older; World Health Organization (WHO) performance status of zero, one or two; life expectancy of at least 6 months; adequate renal function at baseline (serum creatinine ≤3.0 mg/dl or ≤266 μmol/l); and...
stable antineoplastic therapy (including corticosteroids) for at least 4 weeks before starting study medication.

Patients were excluded if they had received previous treatment with bisphosphonates or gallium nitrate within the last 4 months; bone surgery within 5 weeks of screening or any investigational drug within 30 days, radiotherapy within 5 weeks, previous radioisotope therapy within 4 weeks or high-dose chemotherapy within 6 months of starting study medication. Other exclusion criteria included a history of brain metastases; pregnant or breast-feeding; uncontrolled hypercalcemia/hypocalcemia; Paget’s disease of the bone; primary hyperparathyroidism and untreated esophagitis or gastric ulcers.

study design
The primary objective of this multicenter, randomized, open-label, two-arm trial was to assess the efficacy of daily oral ibandronate 50 mg versus i.v. zoledronic acid 4 mg with respect to biochemical markers of bone turnover for up to 12 weeks. The study also compared the safety and tolerability of the two drugs, including the effect on bone pain.

Patients were randomized 1:1 to receive either oral ibandronate (50 mg/day) or i.v. zoledronic acid (4 mg every 4 weeks; 15-minute infusion), for up to 12 weeks. Patients were stratified at randomization according to antineoplastic therapy, i.e. aromatase inhibitors (or goserelin) versus tamoxifen (and other selective estrogen receptor modulators or megestrol) versus cytotoxic therapy (including trastuzumab), and also according to opioid use or not.

The study received Ethics Committee approval and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients gave written, informed consent to their participation in the study.

study assessments
Blood and urine were sampled in fasting patients before intake of study drug for assessment of biochemical markers of bone turnover at screening (<28 days before the start of the study), baseline (predose study day 1) and week 12. The primary end point was mean percentage change in serum levels of the bone resorption marker cross-linked C-terminal telopeptide of type I collagen (S-CTX) at week 12. The normal range of S-CTX (0.126–1.0 ng/ml) was derived from healthy pre- and postmenopausal women (n = 250 and n = 430, respectively). Additional efficacy assessments included urinary levels of CTX (U-CTX) (a marker of bone resorption) and serum levels of the following bone formation markers: bone-specific alkaline phosphate (bone ALP); amino-terminal procollagen propeptide of type I collagen (PINP) and osteocalcin (OC). Intra- and interassay coefficients of variation are <8% for all measurements. All assays were carried out in a specialized central laboratory (Synarc, Lyon, France). Commercial assays used were as follows: S-CTX, Serum β CrossLaps, Roche Diagnostics; U-CTX, CrossLaps® ELISA, Nordic Bioscience Diagnostic; Bone ALP—OSTASE, Access, Beckman-Coulter; PINP, Total PINP, Roche Diagnostics and OC, N-MID Osteocalcin, Roche Diagnostics. CTX was chosen as the preferred marker of bone resorption in this study to facilitate comparisons between previous ibandronate studies measuring CTX. Skeletal-related events were not measured due to the short follow-up time.

Bone pain was measured every 4 weeks using a five-point scoring system (where 0 = no pain and 4 = intolerable pain) [25, 26]. Analgesic consumption was recorded using an adaptation of the scoring system defined by Coleman et al. [26]. Radiotherapy used to treat bone pain was recorded. Safety and tolerability were assessed by recording adverse events, graded on a four-point scale comprising mild, moderate, severe and life threatening by assessing WHO performance status and by clinical laboratory tests carried out at screening, baseline and during the treatment period. Mild adverse events were recorded if ‘discomfort was noticed but no disruption of normal daily activity’; moderate if ‘discomfort was sufficient to reduce or affect daily activity’; severe if there was an ‘inability to work or perform normal daily activity’; life threatening adverse events ’represented an immediate threat to life’.

statistical analyses
Treatment groups each comprising 95 assessable patients at week 12 were required to show equivalence under normal approximation with a power of 80% and two-sided significance of 5%, assuming an equal outcome, a standard deviation of 35% and an equivalence range of ±15%. On the basis of previous studies, a dropout rate of up to 24% was expected, and planned accrual to the study was a total of 250 patients (125 per arm). A change to nonparametric methods was foreseen in case the normal approximation could not be justified.

Biochemical markers of bone turnover were assessed as mean percentage changes from baseline at week 12. Differences between treatment groups in primary end points were analyzed using one-sided Wilcoxon rank tests. Confidence intervals (CIs) (90% for equivalence and 95% for reference to other reports) for the difference between treatments were calculated based on nonparametric Hodges-Lehman estimates because a normal distribution assumption was not fully justified, even after log or similar transformations.

Evaluation of efficacy was based primarily upon analysis of the intention-to-treat (ITT) population, which included all patients who were randomized and who had both baseline and week 12 assessments of S-CTX. The safety analysis population was defined as all patients receiving at least one dose of trial medication and with a safety follow-up, whether withdrawn prematurely or not.

Primary variables and secondary variables were defined within the protocol and the sequence within each category was considered as prioritization. The list of importance is therefore CTX, PINP, osteocalcin, bone ALP (within primary) and bone pain, analgesic use, changes in serum calcium, etc (within secondary). No adjustments were made because of this prioritization or sequential approach.

results

patient demographics
A total of 275 patients from seven countries were recruited and randomized to treatment (Figure 1). With the exception of one patient, randomized to zoledronic acid, who did not receive any study medication, all patients were included in the safety analysis population. Nine patients in the ibandronate group and 12 patients in the zoledronic acid group were excluded from ITT analysis population because the baseline and/or week 12 assessment of bone markers were not available.

The treatment groups were balanced with respect to demographics and all baseline disease characteristics (Table 1) and location of metastases were similar between groups. Multivariate analyses were carried out that included baseline characteristics, but the results remained the same with respect to the comparison of primary end points. Mean baseline pain scores were similar for each treatment group (0.92 versus 0.82 for the ibandronate and zoledronic acid groups, respectively), and moderate to intolerable pain was reported by 26 (19%) patients in the ibandronate group and 19 (13%) patients in the zoledronic acid group. The groups were well balanced in terms of the number and types of concomitant tumor...
WHO, World Health Organization.

Table 1. Baseline demographics and disease characteristics in the safety analysis population

<table>
<thead>
<tr>
<th></th>
<th>Ibandronate 50 mg (n = 137)</th>
<th>Zoledronic acid 4 mg (n = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>55 (29–85)</td>
<td>55 (31–80)</td>
</tr>
<tr>
<td>Median height, cm (range)</td>
<td>162 (149–178)</td>
<td>163 (143–185)</td>
</tr>
<tr>
<td>Mean weight, kg (range)</td>
<td>70 (42–114)</td>
<td>73 (46–124)</td>
</tr>
<tr>
<td>WHO performance status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>31 (23)</td>
<td>38 (28)</td>
</tr>
<tr>
<td>1</td>
<td>88 (64)</td>
<td>91 (66)</td>
</tr>
<tr>
<td>2</td>
<td>16 (13)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Median time since primary disease diagnosis, years (range)</td>
<td>4.1 (0.1–32.7)</td>
<td>3.9 (0.1–35.9)</td>
</tr>
<tr>
<td>Median time since diagnosis of bone metastases, years (range)</td>
<td>0.4 (0.04–18.4)</td>
<td>0.5 (0.03–16.6)</td>
</tr>
<tr>
<td>Previous treatment of breast cancer, n (%)</td>
<td>124 (91)</td>
<td>130 (95)</td>
</tr>
<tr>
<td>Previous radiotherapy, n (%)</td>
<td>96 (70)</td>
<td>94 (69)</td>
</tr>
<tr>
<td>Concomitant treatment of breast cancer, n (%)</td>
<td>130 (95)</td>
<td>129 (94)</td>
</tr>
</tbody>
</table>

WHO, World Health Organization.

Figure 1. Patient disposition.

Very few patients had disease progression in this relatively short study duration. One patient in the ibandronate arm withdrew due to breast cancer progression. A further two patients in the ibandronate arm died during the study due to disease progression. One patient in the zoledronic acid arm died due to a cerebral hemorrhage which was considered related to the underlying malignant disease.

Compliance with oral ibandronate was good. On the basis of returned medication, 97% of patients in the safety population had >90% compliance. In the i.v. zoledronic acid arm, 97% of patients received 100% of study drug.

Efficacy: biochemical markers of bone metabolism and turnover

Both bisphosphonates significantly reduced the primary end point marker of bone resorption, S-CTX, by ~75% at week 12 compared with baseline [P < 0.001 for both versus baseline; mean change from baseline with ibandronate 76% ± 29 [± standard deviation (SD); range −98 to 87] versus zoledronic acid 73% ± 47 (range −99 to 247)] (Figure 2A, Table 2). U-CTX levels were also significantly reduced to a similar extent by both bisphosphonates compared with baseline [P < 0.001 for both versus baseline; ibandronate 78% ± 50 (range −99 to 391) versus zoledronic acid 86% ± 17 (range −98 to 71)] (Figure 2B, Table 2). The reductions in CTX caused by ibandronate and zoledronic acid were considered statistically equivalent for either serum or urinary levels of this bone marker (P < 0.001 for all one-sided noninferiority Wilcoxon tests; the 90% Hodges-Lehman CIs for the difference were −1.7% to 3.0%, and were completely within the noninferiority margin of 15%).

The proportion of patients with high (>1.0 ng/ml), normal (0.126–1.0 ng/m) or low (<0.126 ng/ml) S-CTX levels at week 12 was compared with baseline (Figure 3). In the ibandronate group, S-CTX levels in all patients with high baseline values decreased to normal or low levels by week 12, while S-CTX levels remained high at week 12 in three of 22 patients (13.6%) with high baseline S-CTX levels in the zoledronic acid group. P values of the two-sided Wilcoxon test comparing baseline values with values at week 12 were all ≤0.001 for ibandronate and zoledronic acid within the normal and high baseline S-CTX groups.

The markers of bone formation, bone-specific alkaline phosphatase, PINP and OC, decreased by 26%–47% compared with baseline with both bisphosphonates (Table 2).

There was no significant difference in the mean change (±SD) in bone pain between the treatment groups during either the last week [ibandronate −0.14 ± 0.78 versus zoledronic acid −0.21 ± 0.77, P = not significant (NS)] or last 48 h of the study [ibandronate −0.18 ± 0.78 versus zoledronic acid −0.24 ± 0.77, P = NS]. The change in mean analgesic consumption (±SD) at week 12 compared with baseline was similar in each treatment group (ibandronate −0.05 ± 0.84 versus zoledronic acid −0.11 ± 0.53, P = NS).

Eighteen patients in the ibandronate group and nine in the zoledronic acid group received radiotherapy for the treatment of bone pain during the study (P = 0.07). Of the 27 patients that received radiotherapy, 17 were from one...
site in Russia (10 patients in the ibandronate arm and seven patients in the zoledronic acid arm). The overall difference in patients receiving radiotherapy and analgesia is likely to be due to different clinical practice between centers. The relatively small number of patients precludes meaningful interpretation. The mean WHO performance status score stayed almost constant in each group (ibandronate -0.03 and zoledronic acid 0.02).

Patients in the ibandronate and zoledronic acid groups started with similar baseline serum intact parathyroid hormone (PTH) values. Mean concentrations of intact PTH increased between baseline and week 12 in both treatment groups (ibandronate 20.03%, zoledronic acid 0.02%). No distinct changes regarding electrolytes were observed in either treatment group. Changes from baseline in serum calcium were ±0.04 mmol/l with ibandronate (from 2.47 to 2.42 mmol/l) and ±0.01 mmol/l with zoledronic acid (from 2.44 to 2.43 mmol/l) (Roche standard SI reference range: 2.10–2.60 mmol/l).

Both oral ibandronate 50 mg and i.v. zoledronic acid 4 mg were well tolerated. The proportion of patients who experienced any adverse event seemed lower with ibandronate than with zoledronic acid (65.0% versus 75.9%), as was the incidence of adverse events considered treatment related by the investigator (21.9% versus 51.1%) (Table 3).

There was a lower incidence of adverse events during the first 3 days of the study with oral ibandronate than with i.v. zoledronic acid (8.0% versus 47.5%), including in particular pyrexia and influenza-like symptoms considered probably or possibly related to treatment. The overall incidence of pyrexia was 0% and 16.8% in the ibandronate and zoledronic acid groups, respectively, while influenza-like symptoms were reported in 0.7% and 5.1%, respectively.

Patients in the zoledronic acid group also experienced a higher incidence of treatment-related musculoskeletal and connective tissue disorders (20.4% versus 11.0%), essentially consisting of bone pain (12.4% versus 5.8%) and nervous system disorders (11.0% versus 2.2%, mostly consisting of headaches), while gastrointestinal disorders occurred only slightly more frequently in the ibandronate group (Table 3).

There were no clinically relevant laboratory findings during the study. In particular, there was no evidence of deterioration in renal function in either treatment group as assessed by mean change (±SD) from baseline in serum creatinine (ibandronate -2.2 ± 17.0 μmol/l versus zoledronic acid -1.8 ± 16.0 μmol/l) and in calculated creatinine clearance (ibandronate +2.37 ± 17.23 ml/min versus zoledronic acid +2.86 ± 18.27 ml/min).

The incidence of serious adverse events appeared to be lower with oral ibandronate than with i.v. zoledronic acid (5.8% versus 8.0%).

**discussion**

In this first head-to-head trial, treatment with oral ibandronate was statistically noninferior to zoledronic acid for the primary end point, reduction in the bone resorption marker S-CTX, as well for the reduction in U-CTX and the three bone formation markers. Markers of bone turnover have been shown to correlate with the burden of skeletal disease and, in some studies, with bone pain levels [16, 27]. Analysis of data from three phase III trials of patients treated with zoledronic acid or

**Table 2.** Mean (95% CI) percentage change from baseline in bone turnover markers

<table>
<thead>
<tr>
<th></th>
<th>S-CTX</th>
<th>U-CTX</th>
<th>Bone ALP</th>
<th>PINP</th>
<th>OC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibandronate</td>
<td>-76</td>
<td>-78</td>
<td>-37</td>
<td>-47</td>
<td>-35</td>
</tr>
<tr>
<td></td>
<td>(-81 to -71)</td>
<td>(-87 to -69)</td>
<td>(-43 to -30)</td>
<td>(-55 to -40)</td>
<td>(-39 to -30)</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>-73</td>
<td>-86</td>
<td>-26</td>
<td>-39</td>
<td>-26</td>
</tr>
<tr>
<td></td>
<td>(-81 to -65)</td>
<td>(-90 to -83)</td>
<td>(-43 to -8)</td>
<td>(-52 to -26)</td>
<td>(-43 to -8)</td>
</tr>
</tbody>
</table>

*Mean baseline S-CTX levels in the treatment groups were ibandronate 0.70 ng/ml and zoledronic acid 0.65 ng/ml. CI, confidence interval; S-CTX, serum levels of cross-linked C-terminal telopeptide of type I collagen; U-CTX, urinary CTX; BAP, bone-specific alkaline phosphatase; PINP, amino-terminal procollagen propeptides of type I collagen; OC, osteocalcin.*

original article

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pamidronate revealed that there was a statistically significant correlation between bone marker levels and clinical outcomes (skeletal-related events, disease progression and death) [16]. These analyses support the hypothesis that patients with high levels of N-terminal telopeptide (NTX) of type I collagen (a marker of bone resorption) at baseline or during treatment are at higher risk for negative clinical outcomes, such as the development of skeletal-related events. The type I collagen telopeptide fragments, NTX and CTX, essentially provide similar information [28]. Furthermore, studies have shown that they are positively correlated [29, 30]. Therefore, as the data herein show that oral ibandronate and i.v. zoledronic acid reduce levels of the marker of bone resorption CTX by a similar extent (ibandronate 76% versus zoledronic acid 73%), it may also indicate that they have comparable efficacy for preventing skeletal-related events, although this would need to be demonstrated.

In this study, biochemical markers were measured at baseline and after 3 months, however, no assessments were made to determine early changes. It has been suggested that bone resorption markers fall within a few days of receiving zoledronic acid treatment. Therefore, future studies should determine relative bone marker decreases in the first days/weeks after zoledronic acid and ibandronate treatment as there may be differences between these drugs during this time.

Treatment with oral ibandronate also resulted in a favorable safety profile. More patients experienced adverse events with i.v. zoledronic acid 4 mg than with oral ibandronate 50 mg. In particular, oral ibandronate was associated with a lower incidence of adverse events during the first 3 days; these early adverse events were predominantly due to the acute phase response caused by i.v. administration of zoledronic acid. Neither group showed evidence of deterioration in renal function; however, this was not expected in such a short trial period. A greater incidence of gastrointestinal toxicity may be expected with an oral bisphosphonate compared with an i.v. formulation; however, this was not the case in the present study. Observed gastrointestinal toxicity in the zoledronic acid arm (i.e. upper abdominal pain, oral discomfort,

Table 3. Treatment-related adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Oral ibandronate, n (%)</th>
<th>Intravenous zoledronic acid, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>15 (10.95)</td>
<td>28 (20.44)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>15 (10.95)</td>
<td>11 (8.03)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>5 (3.65)</td>
<td>45 (32.85)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>3 (2.19)</td>
<td>15 (10.95)</td>
</tr>
</tbody>
</table>

Figure 3. Percentage of patients with high, normal or low S-CTX levels at week 12 compared with baseline.
gastrointestinal pain) may not be a direct consequence of drug administration.

For special populations, such as the elderly, treatment-related adverse events influence therapy choice. The apparent overall tolerability of oral ibandronate 50 mg, particularly during the first 3 days of treatment, may provide improved satisfaction with therapy. Oral ibandronate also shows long-term safety. Two phase III, placebo-controlled studies of oral ibandronate and an open-label follow-up study showed that oral ibandronate was well tolerated for up to 4 years of treatment [4, 31]. Furthermore, compliance with oral ibandronate appears to be good [9], and in this trial 97% of patients received >90% of the study drug. The option of convenient home administration with oral ibandronate offers an additional potential advantage, especially for patients treated with oral antineoplastic drugs and/or with decreased mobility who may find it difficult to attend hospital for i.v. infusions.

Bisphosphonate studies have typically analyzed skeletal-related events in order to assess efficacy. However, existing studies have used a variety of different methods to do this, making comparison of results between studies difficult. Measures range from the recording of time to first skeletal event, to more comprehensive analyses of the number of skeletal-related events over time, such as the skeletal morbidity period rate or skeletal morbidity rate. The more robust Andersen–Gill multiple events method [32, 33], which allows for variability of skeletal-related events rates over time and between patients, has been used to analyze trials with zoledronic acid [7] and ibandronate [34]. Clinically important secondary end points, such as bone pain and quality of life, have also been measured using different scales.

While the issue of different methods of measurement would be resolved at least in part by head-to-head comparative bisphosphonate trials, there have been very few of these studies to date, and most phase III bisphosphonate studies have been placebo controlled [35, 36]. A randomized phase III study of i.v. zoledronic acid 4 mg versus i.v. pamidronate 90 mg (every 3–4 weeks for 96 weeks) in patients with breast cancer and multiple myeloma showed no significant difference in skeletal morbidity as measured by the proportion of patients developing a skeletal event, the time to first event and the skeletal morbidity rate, but differences between both drugs clearly emerged only when using the Andersen–Gill multiple events method [7].

With increasing evidence to support the clinical relevance of measuring bone turnover markers in patients with metastatic bone disease, the present head-to-head trial offered a relatively simple and objective way of comparing the efficacy of two widely used bisphosphonates. Although this current study shows that the effects of oral ibandronate and intravenous zoledronic acid on bone markers are equivalent, studies are also underway which will directly compare the effects of these bisphosphonates using the more traditional measure of bisphosphonate efficacy, a reduction in the incidence of skeletal-related events [37, 38].

disclosure of previous presentations


This article has not been published as a primary manuscript, and is not under consideration elsewhere.

acknowledgements

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references