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Ibandronate provides efficacy and safety in the treatment of metastatic bone disease

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ABSTRACT

For patients with metastatic bone disease, preventing disease complications and palliating symptoms are the primary treatment goals. It is therefore essential that a bisphosphonate treatment has proven efficacy in preventing skeletal-related events (SREs). In addition, because patients with advanced cancer have a considerable disease burden and may be experiencing serious treatment-related adverse events (AEs), safety and tolerability should be considered when selecting a bisphosphonate. Ibandronate is a single-nitrogen, noncyclic bisphosphonate available in intravenous and oral formulations. In phase III placebo-controlled trials, both formulations provided similar risk reductions for SREs. In a recent study, ibandronate was at least as effective as zoledronic acid in decreasing serum and urine levels of bone markers (prognostic indicators of SREs). There are important differences in safety and tolerability between ibandronate and zoledronic acid. In comparative studies, ibandronate was associated with a markedly lower incidence of acute-phase reaction AEs than zoledronic acid. Intravenous ibandronate demonstrated a renal safety profile comparable to that of placebo in phase III, whereas there have been numerous reports of renal toxicity or renal failure with zoledronic acid use in clinical practice. The superior renal safety of ibandronate allows high-dose administration over consecutive days (loading dose) for rapid relief of metastatic bone pain. A registration study is currently under way to demonstrate the safety of 15-min ibandronate infusions. Overall, ibandronate has excellent efficacy and safety profiles. Ibandronate use could potentially reduce the incidence of some bisphosphonate-associated AEs among patients with metastatic bone disease.

1. Introduction

The occurrence of bone metastases generally indicates that a cancer has become incurable,[1] so preventing complications and palliating symptoms associated with metastatic bone disease are the primary treatment goals. Several bisphosphonates are available in Europe for treating metastatic bone disease: clodronate, pamidronate, zoledronic acid, and ibandronate. Of these, ibandronate has the broadest range of data demonstrating both rapid and sustained relief of metastatic bone pain.[2–4] However, patients with bone metastases suffer from other skeletal-related events (SREs), including pathological fractures, spinal cord compression, and hypercalcemia of malignancy.[5] It is therefore essential that a bisphosphonate has proven efficacy for preventing SREs. Because patients with advanced cancer have a considerable disease burden and may be experiencing serious treatment-related adverse events (AEs), it is also essential that safety and tolerability be considered in the selection of a bisphosphonate. In this review, efficacy and safety data are summarized for ibandronate, which is available in intravenous and oral formulations.

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2. Efficacy of ibandronate in metastatic bone disease

The efficacy of ibandronate for preventing SREs has been evaluated in three randomized, placebo-controlled phase III trials with patients who had breast cancer and bone metastases.[6,7] One trial evaluated intravenous ibandronate and two identical trials assessed oral ibandronate; the results of these two trials were pooled for analysis as pre-planned. SREs were defined as vertebral fractures, pathological nonvertebral fractures, radiotherapy (for uncontrolled bone pain or impending fractures), or surgery (for fractures or impending fractures). The primary efficacy parameter was the skeletal morbidity period rate (SMPR, defined as the mean number of new SREs occurring within discrete 12-week periods). The use of this more rigorous endpoint minimizes the multiple counting of SREs that occur within close proximity and are likely to be related (e.g., a pathological fracture necessitating surgery).[8] In the trial of intravenous ibandronate, patients receiving 6 mg every 3–4 weeks for 2 years had a significantly lower mean SMPR than placebo-treated patients (1.19 vs 1.48; $P = 0.004$).[7] In addition, ibandronate 6 mg-treated patients had a lower mean number of new SREs per patient (3.64 vs 2.65; $P = 0.032$) and a longer time to first bone event (50.6 weeks vs 33.1 weeks; $P = 0.018$). In multiple-event Poisson regression analysis, a 40% reduction in risk of new bone events was calculated for intravenous ibandronate 6 mg compared with placebo ($P = 0.0033$).[9] In the pooled analysis of oral ibandronate trials, patients who received oral ibandronate 50 mg daily also had a significantly lower mean SMPR than the placebo group (0.95 vs 1.18; $P = 0.004$).[6,10] In addition, the oral ibandronate 50 mg group had a significantly lower incidence of new SREs per patient (1.85 vs 1.15; $P = 0.008$) and a longer time to first new bone event (90.3 weeks vs 64.9 weeks; $P = 0.089$) than the placebo group.[6] Multivariate Poisson regression analysis demonstrated a risk reduction of 38% vs placebo for oral ibandronate 50 mg ($P < 0.0001$).[6] The similar efficacy of oral and intravenous ibandronate in these trials is striking (Fig. 1) and indicates that the choice of formulation can be based on practical considerations and convenience for patient and physician.

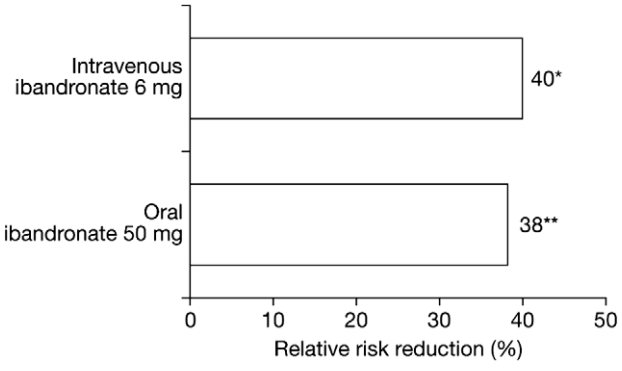

Fig. 1 – Risk reductions for SREs in breast cancer patients treated with intravenous and oral ibandronate: phase III data.[9] *P = 0.0033; **P = 0.0001 (P-values stated are for ibandronate treatment compared with placebo).

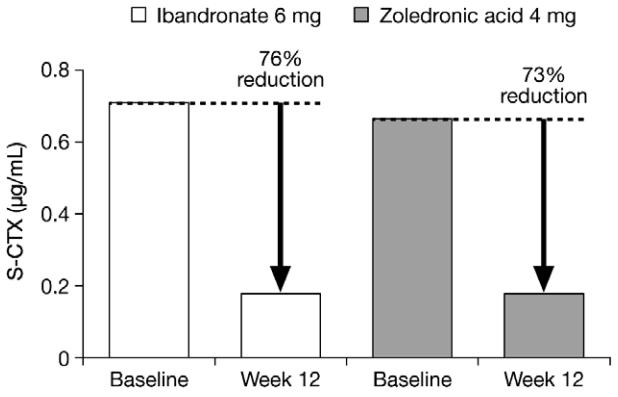

Fig. 2 – In a comparative phase III trial, ibandronate was noninferior to zoledronic acid in reducing serum or urine markers of bone turnover.[15] Data for serum levels of cross-linked C-terminal telopeptide of type I collagen (s-CTX) are shown.

To date, there have been no prospective randomized clinical trials comparing the SRE efficacy of ibandronate and zoledronic acid, the two newest bisphosphonates. Biochemical markers of bone cell activity are useful determinants for assessing clinical responses to therapies for metastatic bone disease, and suppression of bone turnover markers with bisphosphonate therapy correlates with a reduction in SREs.[11–14] A randomized, open-label, phase III study of 254 patients with breast cancer and bone metastases assessed reductions in bone turnover marker levels following 12 weeks of treatment with oral ibandronate 50 mg/day or intravenous zoledronic acid 4 mg every 3–4 weeks.[15] Ibandronate was statistically noninferior to zoledronic acid, with similar reductions observed across several bone turnover markers, including levels of cross-linked C-terminal telopeptide of type I collagen (s-CTX, Fig. 2) and bone-specific alkaline phosphatase. Subgroup analyses showed that ibandronate and zoledronic acid had similar effects regardless of whether patients had high or low concentrations of bone turnover markers at baseline.

Comparative bone turnover marker data suggest that ibandronate and zoledronic acid are likely to reduce the incidence of SREs to a similar extent. In addition, the SRE risk reduction for patients with metastatic breast cancer treated with zoledronic acid as calculated with multivariate Andersen–Gill analysis (41%)[16] is comparable to values calculated for intravenous and oral ibandronate using the same method (29% and 38%, respectively),[17] although cross-trial comparisons should be interpreted with caution.

3. Ibandronate tolerability

There appear to be important differences in tolerability between ibandronate and zoledronic acid, as demonstrated in short-term comparative studies.[18] Safety data were collected during the bone marker trial comparing oral ibandronate and intravenous zoledronic acid in breast cancer patients. In addition, a phase II safety study compared ibandronate and zoledronic acid for patients with breast cancer or multiple myeloma ($n = 77$). In this study, patients received either intravenous ibandronate 6 mg on Day 1 followed by oral ibandro-

Table 1 – Adverse events (AEs) in patients with metastatic bone disease following treatment with ibandronate or zoledronic acid in 2 comparative 12-week trials (P values not stated) [18]

Primary cancer	Trial A		Trial B	
	Breast cancer or multiple myeloma		Breast cancer	
Treatment regimen	Intravenous ibandronate (Day 1) then oral ibandronate daily from Day 2	Intravenous zoledronic acid 4 mg monthly	Oral ibandronate daily	Intravenous zoledronic acid monthly
Total patients	39	38	137	137
Overall AEs (% of pts)	64%	74%	65%	76%
AEs on Days 1–3 (% of pts)	26%	47%	8%	48%
Pyrexia or flu-like symptoms on Days 1–3 (% of pts)	13%	26%	2%	27%

Intravenous infusions with ibandronate or zoledronic acid were administered over 15 min. The incidence of acute-phase reaction AEs was assessed using pyrexia or flu-like symptoms on Days 1–3.

nate 50 mg daily from Day 2 onwards, or standard zoledronic acid treatment (intravenous zoledronic acid 4 mg). In both studies, ibandronate was associated with a lower proportion of patients experiencing AEs (oral ibandronate 65%, zoledronic acid 76%; intravenous-then-oral ibandronate 64%, zoledronic acid 74%; Table 1). In particular, there was a clear difference in reports of AEs on Days 1–3 (oral ibandronate 8%, zoledronic acid 48%; intravenous-then-oral ibandronate 26%, zoledronic acid 47%). Intravenous bisphosphonates are associated with acute-phase reactions (APRs) following first infusion.[19] To compare the two bisphosphonates for APRs, the incidence of pyrexia or flu-like symptoms on Days 1–3 was examined. As expected, oral ibandronate was associated with a much lower incidence of pyrexia or flu-like symptoms than zoledronic acid (2% vs 27%; *P* value not stated; Fig. 3). Furthermore, fewer patients receiving intravenous ibandronate reported pyrexia or flu-like symptoms on Days 1–3 than those receiving zoledronic acid (13% vs 26%; *P* value not stated).

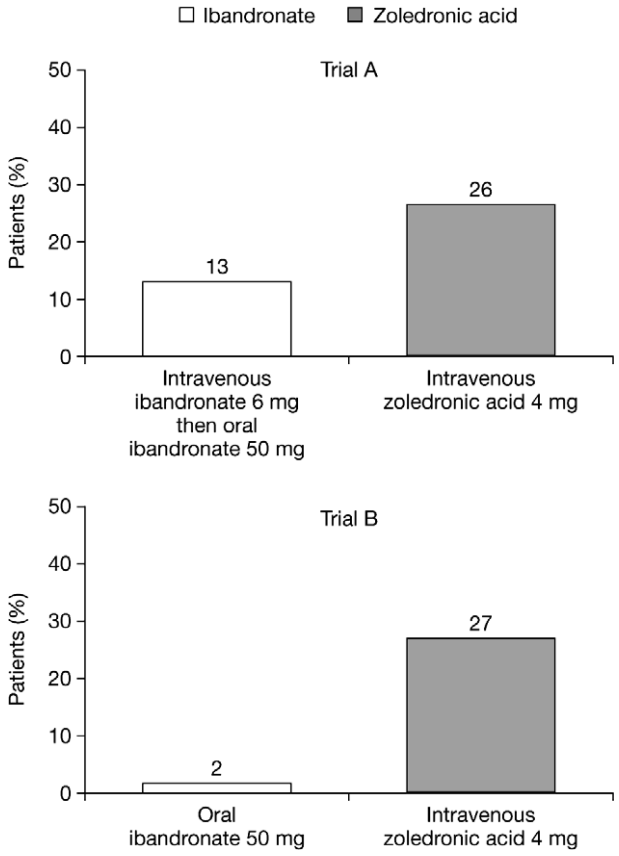

Fig. 3 – Acute-phase reactions (pyrexia or flu-like symptoms) on Days 1 to 3 following ibandronate or zoledronic acid treatment.[18] In trial A, ibandronate was administered as intravenous ibandronate 6 mg on Day 1 followed by oral ibandronate 50 mg on Days 2 and 3. In trial B, ibandronate was administered as oral ibandronate 50 mg on Days 1–3. In both trials, patients in the zoledronic acid group received intravenous zoledronic acid 4 mg on Day 1. *P* values were not stated.

Oral bisphosphonates can be associated with gastrointestinal AEs. In the phase III trials, there was a slightly higher incidence of treatment-related AEs with oral ibandronate 50 mg than with placebo (27% vs 18%).[6] Treatment-related AEs reported by ⩾2% of patients for ibandronate 50 mg vs placebo treatment were dyspepsia (7.0% vs 4.7%), nausea (3.5% vs 1.4%), abdominal pain (2.1% vs 0.7%), and esophagitis (2.1% vs 0.7%), plus hypocalcemia (9.4% vs 5.1%). Overall treatment-related serious AE rates were low and similar between groups. There were no compliance issues or withdrawals related to difficulties with swallowing ibandronate tablets, which was a particular problem in trials of oral clodronate.[20,21]

The tolerability of ibandronate has been confirmed in clinical practice. In a study in Germany of 551 patients with breast cancer receiving 24 weeks' treatment with intravenous or oral ibandronate for metastatic bone disease in clinical practice, ibandronate tolerability was rated as "good" or "very good" by almost all patients (97%) and physicians (98%).[22]

4. Renal safety of ibandronate

Renal toxicity is an important safety issue for cancer patients receiving long-term treatment. Renal toxicity can necessitate discontinuation or alternation of supportive care and anticancer medications. During the 2-year phase III trial, the renal safety of intravenous ibandronate was comparable to that of placebo (Fig. 4).[7,23] In addition, no renal AEs were reported in a 2-year follow-up of patients continuing to receive intravenous ibandronate (total treatment duration up to 4 years), demonstrating the safety of long-term treatment.[24] In the

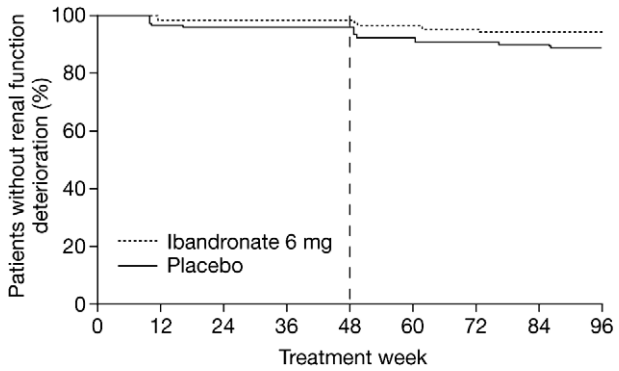

Fig. 4 – In the phase III trial, intravenous ibandronate demonstrated a renal safety profile comparable to placebo.[23]

German study of breast cancer patients receiving 24 weeks of ibandronate treatment in clinical practice, only minor changes in creatinine values were observed during therapy, and no cases of renal failure were reported.[22] In an open-label study performed to assess the renal safety of ibandronate in 21 patients with multiple myeloma and varying degrees of preexisting renal impairment, ibandronate had no effects on serum creatinine or markers of kidney damage.[25]

In contrast to the above findings, there have been numerous reports of renal toxicity or renal failure with intravenous zoledronic acid[26–31] and intravenous pamidronate[28,32–38] that have been fatal in some cases.[26,27] As a direct result, zoledronic acid product labeling has been updated to include renal toxicity warnings, dose reductions for patients with mild to moderate renal impairment (creatinine clearance 30–60 mL/min), and cautions regarding coadministration with other nephrotoxic agents.[39,40] Because of the absence of renal toxicity with intravenous (and oral) ibandronate, there are no nephrotoxicity warnings in product labeling,[41] and ibandronate may be used without dose reductions for patients with mild to moderate renal impairment. Whereas zoledronic acid is contraindicated for patients with severe renal impairment, intravenous ibandronate may be administered at a reduced dose (2 mg). In addition, renal function monitoring prior to each ibandronate dose is not mandatory (unlike with zoledronic acid). Preclinical data support the conclusion that renal toxicity occurs at different frequencies with intravenous ibandronate or zoledronic acid.[42,43]

The superior renal safety of ibandronate allows high-dose administration over consecutive days (loading dose) for rapid relief of metastatic bone pain. Studies have shown no effects on the renal function of patients receiving this dosing regimen,[4,44–47] including a subset of 24 patients with renal insufficiency (baseline serum creatinine 1.8–4.8 mg/dL).[48] Ibandronate is the only intravenous bisphosphonate that can be administered safely as a loading dose. Comparative studies are required to confirm that loading-dose ibandronate provides more rapid pain relief than standard ibandronate dosing.

5. Ibandronate 15-min infusion

The current label for intravenous ibandronate recommends 6 mg infused over 1 h. Shortening the infusion time has potential benefits for resource use as well as patient and physician convenience. In the safety study of intravenous ibandronate followed by oral ibandronate, intravenous infusions were carried out over 15 min and there was no evidence of renal deterioration in creatinine clearance monitoring throughout the 12-week study period.[49] A registration study is currently under way to compare the safety of 15- and 60-min ibandronate infusions with a view to amending product labeling. Results are expected in late 2006.

6. Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) is a rare but serious complication associated with nitrogen-containing bisphosphonates.[50–53] The main symptoms are oral mucosal ulcerations exposing the underlying bone or nonhealing extraction sockets, often presenting with soft tissue infection and pain. The pathogenesis of ONJ is not yet fully understood, although it has been suggested to result from bisphosphonate interference with bone remodeling or anti-angiogenic effects. Management recommendations state that all patients should receive comprehensive dental examinations and preventive dentistry before beginning bisphosphonate therapy, and dental interventions should be avoided once treatment has commenced.[50] To date, the vast majority of ONJ cases have been associated with zoledronic acid or pamidronate treatment.[50] It has been estimated that ONJ may develop in 10% and 4% of patients with multiple myeloma treated with 36 months of zoledronic acid and pamidronate, respectively.[51] There have been too few cases of ibandronate-associated ONJ to date for conclusions to be drawn. Among approximately 720,000 patients treated with ibandronate worldwide, 18 cases of ONJ have been identified so far, and in half of these cases the patients had received other bisphosphonates previously (Roche, data on file). The low number of cases might be related to exposure. Further studies are required to determine the relative incidence of ONJ with each bisphosphonate.

7. Discussion

Available data suggest that the newer bisphosphonates ibandronate and zoledronic acid have comparable efficacy in preventing SREs in patients with metastatic breast cancer. Cross-trial comparisons of phase III multiple-event analysis data show similar risk reductions with both agents. In addition, ibandronate and zoledronic acid have demonstrated comparable efficacy for reducing levels of bone turnover markers, which are prognostic indicators of skeletal complications. The two bisphosphonates differ, however, with respect to their safety profiles. Short-term comparative studies have demonstrated that both oral and intravenous ibandronate are associated with a markedly lower incidence of APR AEs than zoledronic acid. There are also important differences in renal safety with the two bisphosphonates. Whereas ibandronate has demonstrated a renal safety profile comparable to placebo with no treatment-related renal issues reported in clinical practice, zoledronic acid has been associated with numerous reports of renal toxicity and failure. As a result, zoledronic acid product labeling contains several cau-

tions relating to renal safety issues, whereas ibandronate product labeling does not. The renal safety profile of ibandronate allows the use of a loading dose for relief of metastatic bone pain, which is not recommended with other intravenous bisphosphonates. Clinical trials are nearing completion that will likely lead to the recommended infusion time for intravenous ibandronate being reduced from 1 h to 15 min. Several reports have identified ONJ as a severe complication particularly associated with zoledronic acid or pamidronate treatment. Because of the small number of ONJ cases associated with ibandronate, it is too early to draw conclusions regarding the relative incidence versus other bisphosphonates. In general, the relative safety of different bisphosphonates would be more accurately determined by large-scale comparative studies, particularly for renal safety or ONJ. However, it appears from available data that ibandronate has excellent efficacy and safety profiles. In particular, the safety of ibandronate has the potential to decrease management issues associated with bisphosphonate treatment of metastatic bone disease.

Conflict of interest statement

The author has served as a consultant for Roche and Schering-Plough, received research funds from Bristol-Myers Squibb, Novartis, and Roche, and received honoraria from Amgen, Novartis, Roche, and Schering-Plough.

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