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Ibandronic Acid

A Review of its Use in the Treatment of Bone Metastases of Breast Cancer

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Data Selection

Sources: Medical literature published in any language since 1980 on 'ibandronic acid', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE search terms were 'ibandronate' or 'ibandronic acid' and 'breast cancer' or 'breast neoplasms'. EMBASE search terms were 'ibandronate' or 'ibandronic acid' and 'breast cancer'. AdisBase search terms were 'ibandronic acid' or 'ibandronate' and 'breast cancer'. Searches were last updated 30 March 2006.

Selection: Studies in patients with breast cancer and metastatic bone disease who received ibandronic acid. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Ibandronic acid, breast cancer, metastatic bone disease, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability, quality of life.

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Summary

Abstract

Ibandronic acid (Bondronat®) is a potent, new-generation, nitrogen-containing bisphosphonate, available in both intravenous and oral formulations, which effectively inhibits osteoclast-mediated bone resorption. In clinical trials, the two formulations were equally effective in preventing skeletal-related events and improving quality of life in patients with bone metastases of breast cancer. Both intravenous and oral ibandronic acid reduced metastatic bone pain scores below baseline levels for up to 2 years. Oral ibandronic acid is administered as a single 50mg tablet taken once daily. It suppressed bone resorption in breast cancer patients with bone metastases to an extent similar to that observed with intravenous zoledronic acid. Both intravenous and oral ibandronic acid were well tolerated with no evidence of renal toxicity. Ibandronic acid is therefore a valuable addition to the bisphosphonates used in the treatment of bone metastases of breast cancer, offering high potency and the convenience of oral administration, combined with the absence of renal toxicity.

Pharmacological Properties

Ibandronic acid inhibits the bone resorption activity of osteoclasts in osteolytic metastatic bone lesions. Being a nitrogen-containing bisphosphonate, it induces apoptosis in osteoclasts by interfering with the mevalonate pathway and inhibiting farnesyl pyrophosphate synthase. The antiresorptive potency of ibandronic acid in rats was 50-fold higher than that of pamidronic acid and 500-fold higher than that of clodronic acid.

Ibandronic acid may also have direct antiproliferative effects on tumour cells. Animal and *in vitro* experiments suggest that the drug may inhibit tumour cell adhesion and invasion, induce tumour cell apoptosis, reduce the tumour burden and inhibit angiogenesis.

Ibandronic acid rapidly binds to bone (40–50% of the circulating drug), particularly at sites of bone remodelling, or is eliminated. The absorption of oral ibandronic acid is poor and severely impaired by food and drink. The oral bioavailability was 0.44% when administered 30 minutes prior to food or drink. Ibandronic acid is not metabolised and any drug not bound to bone is eliminated by the kidneys and excreted unchanged in the urine with a half-life of approximately 10–14 hours after intravenous administration.

Therapeutic Efficacy

Intravenous ibandronic acid 6mg every 3–4 weeks in patients with breast cancer and bone metastases produced a significant 20% reduction relative to placebo in the overall skeletal morbidity period rate (SMPR) over 96 weeks, which equated to a 40% reduction in the relative risk of skeletal-related events. Intravenous ibandronic acid 2mg was not significantly different from placebo.

Oral ibandronic acid 50mg once daily for 96 weeks in patients with bone metastases of breast cancer similarly reduced the overall SMPR by 18% compared

with placebo, equating to a reduction in the relative risk of skeletal-related events of 38% relative to placebo. Clinical benefit was accompanied by improvements in biochemical markers of bone turnover.

Intravenous ibandronic acid 6mg and oral ibandronic acid 50mg each significantly improved patients' health-related quality of life in the 96-week clinical trials.

Oral ibandronic acid 50mg once daily and intravenous zoledronic acid 4mg every 4 weeks similarly and significantly reduced biochemical markers of bone turnover after 12 weeks in patients with breast cancer and bone metastases, suggesting they would have similar efficacy in preventing skeletal-related events.

Tolerability

Ibandronic acid was well tolerated throughout 4 years of use. In clinical trials, the only notable adverse events with an incidence higher than placebo were flu-like syndrome, myalgia and diarrhoea with intravenous ibandronic acid 6mg and hypocalcaemia, dyspepsia, nausea and oesophagitis with oral ibandronic acid 50mg. There was no evidence of renal toxicity with intravenous or oral ibandronic acid.

1. Introduction

Bone metastases are often associated with advanced cancer and are most common with breast, prostate and thyroid carcinomas and multiple myeloma.[1,2] Bone metastases are present in 65–75% of patients with advanced (metastatic) breast cancer.[2] Metastatic bone lesions may be lytic or sclerotic in nature depending upon whether increased osteoclastic or osteoblastic activity predominates; if both processes are equally active, they are termed mixed lesions.[2] Bone metastases in breast cancer patients usually involve osteolytic disease, where normal bone homeostasis is disrupted and skewed towards excessive resorption of bone.[1,2] Tumour-induced skeletal damage is mediated by osteoclasts that are stimulated directly or indirectly to dissolve bone by local factors (e.g. prostaglandin E, interleukin-1, tumour necrosis factor and procathepsin D) released by tumour cells or associated immune cells, or by systemic factors, such as parathyroid hormone-related peptide.[2] The most frequently affected skeletal sites are the vertebrae, pelvis, ribs, femur and skull.[1] Patients with bone metastases experience considerable morbidity, including bone pain, pathological fractures, hypercalcaemia, reduced mobility and spinal cord or nerve root compression.[2]

Bisphosphonates have proven to be valuable additions to the existing treatment options for metastatic bone disease, consisting primarily of analgesics, radiopharmaceuticals, radiotherapy and surgery.[3-5] Bisphosphonates inhibit the bone resorption activity of osteoclasts and thereby reduce skeletal-related events (bone complications), relieve pain and prevent loss of mobility.[3-6]

Ibandronic acid (Bondronat®)[1] is a highly potent, new-generation, nitrogen-containing bisphosphonate that has long been used in the treatment of osteoporosis and hypercalcaemia of malignancy. It has recently been approved in the EU in both an intravenous and oral formulation for the prevention of skeletal-related events in breast cancer patients with bone metastases.[7] This review focuses on the use of intravenous and oral ibandronic acid to prevent skeletal-related events in breast cancer patients with metastatic bone disease.

2. Pharmacodynamic Properties

As with all bisphosphonates, ibandronic acid is a pyrophosphate analogue having a P-C-P structure (instead of P-O-P) that is resistant to hydrolysis and

1 The use of trade names is for product identification purposes only and does not imply endorsement.

binds with high affinity to the bone mineral, hydroxyapatite, and concentrates in bone, especially at sites of active bone remodelling.[8] The potency and properties of bisphosphonates are governed by the nature of the chemical moiety attached to the central carbon atom.[1] Newer-generation, nitrogen-containing bisphosphonates (aminobisphosphonates) have a different mechanism of action (inhibition of the mevalonate pathway) to first-generation non-aminobisphosphonates (inhibition of adenosine triphosphate [ATP]-dependent enzymes).[1] Ibandronic acid is a so-called third-generation aminobisphosphonate with a side chain consisting of a long, nitrogen-containing, 7-carbon alkyl chain.[8,9]

2.1 Effects on Bone Resorption

The key pharmacological action of bisphosphonates is that they actively inhibit the bone resorption activity of osteoclasts.[10,11] The exact mechanism of action of bisphosphonates is not clear; they have direct inhibitory effects on osteoclasts, they reduce the recruitment and binding of osteoclast precursors, they induce apoptosis of osteoclasts and can modify osteoclast function by acting on osteoblasts.[9,12]

Ibandronic acid is a nitrogen-containing bisphosphonate and therefore induces apoptosis of osteoclasts by interfering with the mevalonate pathway and inhibiting farnesyl pyrophosphate synthase and hence the generation of geranylgeranyl pyrophosphate.[8] Geranylgeranyl pyrophosphate is required to prenylate certain guanosine triphosphate (GTP)-binding proteins, such as Rho, Rac and Rab, which are essential for maintaining the cytoskeletal structure of the osteoclast.[13]

In terms of relative potency, ibandronic acid inhibited arotinoid-stimulated bone resorption in thyroparathyroidectomised rats with a potency twice that of risedronic acid, 10 times higher than that of alendronic acid, 50 times higher than pamidronic acid and 500 times higher than clodronic acid.[14] When administered orally, it displayed only 1% of the level of activity seen after subcutaneous administration.[14] Unstimulated endogenous bone resorption was also inhibited by ibandronic acid, resulting in an increase in bone density and volume.[14]

Ibandronic acid (4 μg/day subcutaneously) significantly ($p < 0.01$) inhibited the radiological progression of osteolytic bone metastases induced by the intracardiac injection of MDA-MB-231 human breast cancer cells in mice.[15,16] Similarly, subcutaneous ibandronic acid 0.003mg phosphorous per kg daily for 28 days significantly preserved bone density ($p < 0.001$) and bone stability ($p < 0.01$–0.001) in rats bearing bone implants of Walker 256 carcinosarcoma cells.[17] In a rat model of osteolytic bone metastases induced by inoculation with human breast cancer cell line MDA-MB-231, ibandronic acid not only prevented the development of new osteolytic lesions, but with existing small lesions it induced a negative growth rate indicating a reversal in tumour growth.[18]

In mice injected intracardiacly with MDA-MB-231 cells, the number of osteoclasts was dramatically decreased ($p < 0.0001$) and the proportion of apoptotic osteoclasts was markedly increased ($p < 0.0001$) in the bone of ibandronic acid-treated (4 μg/day) mice.[15]

However, in a non-tumour rat model of bone resorption, at dosages of ibandronic acid that strongly inhibited bone resorption (phosphorous 0.01 and 0.1 mg/kg of bodyweight), the number of osteoclasts on the bone surface was actually increased, suggesting that the drug did not act by decreasing osteoclast recruitment. Osteoclast numbers were reduced only with high concentrations of the drug (phosphorous 1 mg/kg).[14]

2.2 Effects on Tumour Cells

In addition to inhibiting the resorption activity of osteoclasts, bisphosphonates may also have direct inhibitory effects on tumour cells and may inhibit tumour invasion by preventing tumour cell adhesion to the bone matrix.[9] It has also been suggested that bisphosphonates may inhibit bone metastases by direct inhibitory effects on the angiogenesis that is essential for the growth of metastases.[19]

In the mouse model of osteolytic bone metastases induced by the intracardiac injection of MDA-MB-231 cells, ibandronic acid significantly ($p < 0.0001$) reduced the tumour burden in bone and

significantly ($p < 0.0001$) increased the number of apoptotic MDA-MB-231 cells in bone metastases, while not affecting the level of mitotic cells.[15] These effects were not seen in tumours at the orthotopic site (mammary fat pads), indicating that they were specific to bone or that drug concentrations were possibly too low to be effective in visceral organs compared with bone.[15,20]

In contrast to studies showing an effect of the drug on tumour cell burden, high dosages of ibandronic acid (0.16 mg/kg/day) significantly reduced the occurrence of osteolytic bones lesions, but had no significant effect on total tumour cell burden in a mouse model of myeloma bone disease.[21]

Pretreating bovine cortical bone slices or cryostat sections of murine developing trabecular bone with ibandronic acid (10^{-6} to 10^{-4} mol/L) dose-dependently prevented the adhesion of MDA-MB-231 breast cancer cells *in vitro*. Across the same concentration range, inhibition was also seen with olpadronic acid, alendronic acid and pamidronic acid, but not with etidronic acid or clodronic acid.[22]

Ibandronic acid inhibited the adhesion of human breast, prostate or osteosarcoma tumour cells to unmineralised extracellular matrices produced by cultured osteoblastic cells and to bovine cortical bone slices *in vitro*.[23] Ibandronic acid did not exert any cytotoxic effects on tumour cells at the concentration (5×10^{-12} mol/L) used to inhibit adhesion.[23]

Ibandronic acid also inhibited breast carcinoma cell invasion in an *in vitro* model, although cell migration was not inhibited.[24] Ibandronic acid, clodronic acid and zoledronic acid equipotently inhibited the proteolytic activity of matrix metalloproteinase (MMP)-2, MMP-9 and MMP-12.[24] These MMPs are required for digestion of basement membranes to allow tumour cell invasion. However, the clinical significance of this observation is uncertain since tumour invasion was inhibited at much lower concentrations (50% inhibitory concentration [IC_{50}] of 10^{-12} mol/L) than MMP activity (IC_{50} values of $40–160 \times 10^{-6}$ mol/L) and the three bisphosphonates were not equipotent at inhibiting invasion.[24]

Ibandronic acid and other bisphosphonates (pamidronic acid, clodronic acid and zoledronic acid) have also been shown to directly inhibit the growth of cultured human breast cancer cell lines.[25] They dose-dependently induced apoptosis in MCF-7 cells (that appeared to be at least partly mediated by caspases) and necrosis in T47D cells.[25]

2.3 Treatment Regimen Considerations

Preventive treatment for 26 days prior to implantation and stopping at the time of the implant was as effective as therapeutic treatment for 28 days (beginning at the time of implant) in preserving bone density and strength in rats bearing bone implants of Walker 256 carcinosarcoma cells.[26] Treatment both before and after implantation was most effective.

Preventive treatment with ibandronic acid of mice subsequently injected intracardiacly with a subclone of MDA-MB-231 tumour cells that routinely metastasised to both the bone and adrenal glands profoundly reduced osteolytic bone metastases, but did not reduce and even increased metastases to the adrenal glands.[20] However, this model lacks the normal metastasising process to soft tissues.

Intracardiac injection of MCF-7 estrogen-dependent human breast cancer cells in female nude mice produces bone metastases that are initially osteolytic, but which progressively become osteosclerotic over time.[20] Early treatment with ibandronic acid prevented the development of osteosclerotic bone metastases, whereas late treatment beginning 6 weeks after tumour cell inoculation did not inhibit osteosclerotic metastases.[20]

Combined treatment with bisphosphonates and anticancer agents appears to produce additive or synergistic effects. In MDA-MB-231 tumour-bearing mice, combined treatment with ibandronic acid and doxorubicin more effectively suppressed bone and adrenal metastases than either treatment alone.[20] Similarly, other bisphosphonates (incadronic acid and zoledronic acid) combined with tegafur/uracil inhibited bone, lung and liver metastases with additive effects.[20] Ibandronic acid enhanced in an additive manner the growth-inhibitory

actions of antiestrogens on estrogen receptor-positive breast cancer cell lines *in vitro*.[27]

Concomitant treatment of MDA-MB-231-inoculated mice with both ibandronic acid and an inhibitor of MMPs was also more effective than either treatment alone in preventing the development of osteolytic lesions and resulted in no radiologically detectable osteolytic lesions.[16]

2.4 Renal Effects

Intermittent intravenous administration every 3 weeks for 6 months with a minimally nephrotoxic dose of ibandronic acid (1 mg/kg) in rats, did not result in any cumulative renal damage at 6 months.[28] The chosen dose produced minimal-to-slight histological damage to the proximal convoluted tubules 4 days after administration in 60% of animals without affecting clinical laboratory parameters of kidney function. Therefore, this nephrotoxicity induced by ibandronic acid appeared to resolve in the interval between doses.[28]

In contrast, intermittent administration of zoledronic acid (3 mg/kg) did result in the accumulation of renal damage at 6 months that was confirmed by biochemical parameters.[28] A lower 1 mg/kg dose of zoledronic acid, which did not show histological evidence of kidney damage after a single dose, also resulted in cumulative renal damage over 6 months. The difference in nephrotoxicity between the agents was hypothesised to result from zoledronic acid having a longer elimination half-life from renal tissue, especially the proximal convoluted tubules, than ibandronic acid (150–200 vs 24 days).[28,29]

3. Pharmacokinetic Properties

Ibandronic acid can be administered intravenously (6mg infused over 1 hour every 3–4 weeks) or orally (50mg once daily) in the treatment of bone metastases in breast cancer patients (see section 7).[30] The two dosage regimens are considered to be effectively dose-equivalent and essentially interchangeable with respect to therapeutic efficacy (see section 4.1),[31] but there is little published pharmacokinetic information on these dosages in breast cancer patients with metastatic bone disease. Most data derive from regulatory or product information documents[30,32] or published overviews[8,31] and relate to the pharmacokinetics of ibandronic acid in healthy volunteers, including postmenopausal women, or patients with multiple myeloma.

3.1 Absorption and Distribution

The pharmacokinetics of ibandronic acid are dose-proportional after intravenous administration. Following the slow intravenous infusion of ibandronic acid 6mg over 1–2 hours, the mean area under the serum concentration-time curve extrapolated from time zero to infinity (AUC_∞) was 908 ng • h/mL in healthy postmenopausal women and 866 ng • h/mL in patients with multiple myeloma.[8] The respective volumes of distribution were 137 and 101L.[8] The mean maximum serum concentration (C_{max}) observed in healthy postmenopausal women was 328 ng/mL.[32]

Oral ibandronic acid is poorly absorbed with an absolute bioavailability of 0.63% when administered at least 2 hours before food. The drug displays high inter- and intrapatient variability in AUC and is not truly dose proportional, although the C_{max} and AUC are similar between studies using the same dose.[8] Following oral single-dose administration of ibandronic acid 50mg in healthy male volunteers, the mean AUC_∞ was between 29 and 36 ng • h/mL in four separate studies and the mean C_{max} was 11–12 ng/mL.[8] Absorption is believed to occur in the upper gastrointestinal tract and was rapid, with a mean time to C_{max} of 0.8–1.2 hours in the four studies.[8]

The oral absorption of ibandronic acid is severely impaired by the consumption of food or liquids other than plain water.[30] Compared with a fasting state, the bioavailability of oral ibandronic acid is reduced by approximately 90% when taken with a standard breakfast and is reduced by about 30% when taken 30 minutes before a meal, but is not reduced when taken 60 minutes prior to a meal.[30] The bioavailability of ibandronic acid is reduced by about 75% when administered 2 hours after a

meal.[30] Therefore, it is recommended that oral ibandronic acid be taken after an overnight fast of at least 6 hours and at least 30 minutes before eating or drinking.[30]

Thirty minutes of fasting after drug administration was considered more realistic and practical than 60 minutes in order to aid compliance and, therefore, the oral dosage was adjusted on this basis to provide equivalence to the recommended intravenous dosage.[31] The bioavailability of a 50mg daily oral dose administered 30 minutes prior to food or drink was 0.44%, and this dosage provided a median steady-state AUC value similar to that of intravenous ibandronic acid 6mg administered monthly (1548 vs 1155 ng • h/mL).[31] When a 30-minute post-dose fasting time is observed, the clinical efficacy of oral ibandronic acid 50mg once daily is similar to that of intravenous ibandronic acid 6mg every 3–4 weeks (section 4.1).

Ibandronic acid rapidly binds to bone or is eliminated.[30] Animal studies with intravenous radiolabelled ibandronic acid demonstrated that 40–50% of the dose was found in the bone, predominantly trabecular bone, within 2 hours of administration and <2% of the dose was found in non-calcified tissues.[33] After 1 year, approximately 18% of the administered dose of radioactivity was still present in the animal.[33]

Approximately 87% of the drug is bound to human plasma proteins at therapeutic concentrations, while binding to erythrocytes and platelets is very low.[8,30]

3.2 Metabolism and Elimination

Ibandronic acid is not metabolised and has no affinity for the major cytochrome P450 isoforms.[8,30] The majority of the oral dose is not absorbed and is eliminated unchanged in the faeces.[8,30] With an intravenous dose and the absorbed fraction of an oral dose, any drug that is not bound to bone (estimated at 40–50% of the circulating drug) is eliminated by the kidneys and excreted unchanged in the urine.[8,30]

Following intravenous infusion of ibandronic acid 6mg in healthy postmenopausal women or patients with multiple myeloma, the total clearance was 112–120 mL/min and the renal clearance was 59 mL/min, with the difference considered to reflect uptake by bone.[8,30] The proportion of the intravenous dose excreted unchanged in urine was 45–50% and the elimination half-life was 10–14 hours.[8]

Following single-dose oral administration of ibandronic acid 50mg in healthy men in four phase I studies, the renal clearance was 79–112 mL/min, the elimination half-life was 1.3–12 hours and the proportion of the dose excreted unchanged in urine was 0.28–0.40%.[8]

In subjects with mild or moderate renal impairment (creatinine clearance 40–70 mL/min) or severe renal impairment (creatinine clearance <30 mL/min), the total clearance of orally administered ibandronic acid was reduced to 81 or 44 mL/min, respectively (compared with 129 mL/min in subjects with normal renal function).[8] The AUC was increased from 68 ng • h/mL in subjects with normal renal function to 105 and 201 ng • h/mL in subjects with mild-to-moderate or severe renal impairment, respectively.[8,30]

4. Therapeutic Efficacy

The therapeutic efficacy of ibandronic acid in breast cancer patients with metastatic bone disease has been assessed in three randomised, double-blind, placebo-controlled, parallel-group, multicentre, 96-week trials, one of which assessed intravenous ibandronic acid 2 and 6mg every 3–4 weeks (MF 4265), while the other two assessed oral ibandronic 50mg once daily (MF 4434 and MF 4414). Studies MF 4265[34] and MF 4434[35] are fully published. Study MF 4414 has not been published in isolation, but the key data are available in the scientific discussion component of the European Medicine Agency's European Public Assessment Report for Bondronat®.[32] A pooled analysis of the two oral ibandronic acid studies, which was predefined in the study protocols, has been fully published.[36]

In addition to these placebo comparisons, the efficacy of oral ibandronic acid has been compared with that of intravenous zoledronic acid in a

randomised, open-label, 12-week trial, although the study has only been published in abstract form and used biochemical markers of bone turnover, rather than clinical skeletal-related events, to assess response.[37]

4.1 Placebo Comparisons

All patients enrolled in placebo-controlled trials were women aged ≥18 years with histologically confirmed breast cancer, radiologically confirmed bone metastases and WHO performance status ≤2.[34-36]

The primary efficacy parameter in all placebo comparison trials was the skeletal morbidity period rate (SMPR) for all new skeletal-related events (overall SMPR), which consisted of the number of 12-week periods during which new skeletal-related events occurred divided by the total number of 12-week periods on study.[34-36] The rate was adjusted for early withdrawal, avoiding a situation in which the numerator could be zero, by adding 1 to the numerator and 0.5 to the denominator in all instances. Skeletal-related events were defined as vertebral fractures, pathological non-vertebral fractures, radiotherapy for bone complications (pain or impending fracture) or surgery for bone complications (fractures or impending fractures).[34-36]

4.1.1 Intravenous Administration

Intravenous ibandronic acid 6mg every 3–4 weeks for up to 96 weeks significantly reduced the overall SMPR by 20% compared with placebo ($p = 0.004$), while the overall SMPR with the 2mg dose was not significantly different from that with placebo (table I).[34] The reduction in overall SMPR by ibandronic acid 6mg was predominantly the result of reductions in vertebral fractures and skeletal-related events requiring radiotherapy (table I).[34]

Ibandronic acid 6mg, but not 2mg, significantly ($p < 0.05$) reduced the mean number of skeletal-related events per patient (table I) and significantly increased the median time to the first new bone event compared with placebo (50.6 vs 33.1 weeks; $p = 0.018$). The median time to the first new bone event with ibandronic acid 2mg was not statistically significantly different from that with placebo (44.6 vs 33.1 weeks).[34]

Table I. Efficacy of ibandronic acid (IBA) in the prevention of skeletal-related events in patients (pts) with breast cancer and bone metastases. Results from randomised, double-blind, placebo (PL)-controlled, parallel-group, multicentre, 96-week studies

Study	Treatment (mg)	No. of pts[a]	Skeletal morbidity period rate[b]					Mean no. of skeletal-related events per pt
			all new skeletal-related events[c]	vertebral fractures	non-vertebral fractures	events requiring radiotherapy	events requiring surgery	
Intravenous administration (every 3–4 weeks)								
Body et al. (Study MF 4265)[34]	IBA 2[d]	154	1.31	0.70*	0.70	0.95	0.50*	4.24
	IBA 6[e]	154	1.19**	0.71*	0.72	0.91*	0.56	2.65*
	PL	158	1.48	0.82	0.81	1.09	0.62	3.64
Oral administration (once daily)								
Body et al.[36] [f]	IBA 50	287	0.95**	0.58[g]	0.58[g]	0.73***	0.47*	1.15**
	PL	277	1.18	0.63[g]	0.60[g]	0.98	0.53	1.85

a Intent-to-treat populations.

b The number of 12-week periods with new skeletal-related events divided by the number of 12-week periods on study (adjusted for early withdrawal).

c Primary endpoint.

d Administered as a bolus injection.

e Administered as an infusion over 1–2h.

f Pooled analysis of two randomised, double-blind, placebo-controlled, multicentre, phase III trials as predefined in the study protocols.

g Values estimated from a histogram.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs PL.

Bone pain scores were significantly reduced from baseline at 96 weeks by ibandronic acid 6mg (−0.28; $p < 0.001$), but were elevated from baseline with ibandronic acid 2mg (+0.21) and placebo (+0.19).[38] Analgesic consumption increased in all groups and the mean absolute change from baseline in analgesic consumption scores for ibandronic acid 2mg and 6mg (0.89 and 0.51) were not significantly different from that with placebo (0.90).[38]

Only 40% of patients completed 96 weeks of treatment and the median treatment durations were 18.1 months for ibandronic acid recipients and 13.1 months for placebo recipients.[34] The median overall survival times (Kaplan-Meier estimates) with ibandronic acid 2mg (116.4 weeks) and 6mg (113.3 weeks) were not significantly different from that with placebo (106.7 weeks).[38]

4.1.2 Oral Administration

Oral ibandronic acid 50mg administered once daily for 96 weeks significantly ($p < 0.01$) reduced the overall SMPR by 18% compared with placebo in a predefined pooled analysis of two identically designed phase III studies (table I).[36] The reduction in overall SMPR was primarily the result of a reduction in the number of skeletal-related events requiring radiotherapy and, to a smaller extent, a reduction in the number of events requiring surgery.[36]

The pooled analysis omitted skeletal-related events occurring in the first 12 weeks, as being events occurring too early to have been prevented by oral ibandronic acid therapy. However, when the early events were included, the overall SMPR (0.99 vs 1.15; $p = 0.041$) and that for events requiring radiotherapy (0.80 vs 0.98; $p < 0.004$) were still significantly reduced compared with placebo.[36]

Compared with placebo, ibandronic acid 50mg significantly reduced the mean number of events per patient (1.15 vs 1.85; $p = 0.008$) and the per-patient number of 12-week periods with events (0.71 vs 0.99; $p = 0.015$), but not the percentage of patients with events (45 vs 52; $p = 0.122$).[36] Multivariate Poisson regression analysis demonstrated a 38% reduction in the risk of skeletal-related events for ibandronic acid 50mg versus placebo ($p < 0.0001$), which is similar to the 40% risk reduction versus placebo seen with intravenous ibandronic acid 6mg in study MF 4265.[32] Ibandronic acid 50mg delayed the median time to first new bone event compared with placebo, but the difference did not reach statistical significance (90 vs 65 weeks; $p = 0.089$).[36]

Mean bone pain scores at 96 weeks were significantly reduced from baseline with ibandronic acid 50mg compared with placebo (−0.10 vs +0.20; $p = 0.001$).[39] Ibandronic acid maintained bone pain scores below baseline levels throughout the 2-year study, while those with placebo progressively increased.[39] The mean increase in analgesic use scores over 2 years for ibandronic acid recipients was significantly lower than that for placebo recipients (0.60 vs 0.85; $p = 0.019$).[39]

With regard to the individual studies, the results from one study (MF 4434) were essentially the same as those from the pooled analysis,[35] while the results from the other (MF 4414) did not show superiority of oral ibandronic acid over placebo for the primary endpoint, presumably as a result of imbalances in the treatment groups.[32] However, when regression analysis was used to overcome confounding factors in study MF 4414, it demonstrated a 39% reduction in the risk of skeletal-related events for ibandronic acid 50mg versus placebo.[32]

At the end of treatment, there were improvements in biochemical markers of bone turnover.[35,36] The median change from baseline in the urinary concentration of crosslinked C-terminal telopeptide of type I collagen (CTX) was significantly lower with ibandronic acid 50mg than with placebo (−77% vs +11%; $p < 0.001$).[36]

4.1.3 Health-Related Quality of Life

Health-related quality of life was assessed in study MF 4265 (intravenous ibandronic acid 2 and 6mg) using the 30-item European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30).[38] Overall quality-of-life scores based on the five functional domains (physical, emotional, social, cognitive and role) decreased less between baseline and last assessment with ibandronic acid 6mg than with placebo (−10.3 vs −45.4; $p = 0.004$), but the decrease with ibandronic acid 2mg was not significantly different

from that with placebo (−18.1 vs −45.4; p = 0.067).[38] Ibandronic acid 6mg was superior to placebo ($p < 0.05$) with respect to scores in the physical, emotional and social functioning domains, as well as in the global health status component.[38]

Although all symptom scores had improved at the last assessment in patients receiving ibandronic acid 6mg compared with placebo recipients, the differences were only statistically significant ($p < 0.05$) for fatigue and pain (not for nausea and vomiting, diarrhoea, dyspnoea, insomnia, appetite loss or constipation).[38] Only constipation was significantly ($p < 0.05$) reduced versus placebo by ibandronic acid 2mg.

Pooled data from the two oral treatment trials (MF 4434 and MF 4414) indicated that ibandronic acid 50mg once daily for 96 weeks significantly improved the global quality-of-life scores relative to placebo on the EORTC QLQ-C30 questionnaire (−8.3 vs −26.8; p = 0.032).[39] With respect to the five individual functional domains, ibandronic acid 50mg significantly improved the role function ($p \leq 0.01$) and physical function ($p \leq 0.05$) scores.[39]

4.2 Comparison with Zoledronic Acid

In women with advanced breast cancer, radiologically confirmed bone metastases and a WHO performance status ≤2, the efficacy of oral ibandronic acid 50mg once daily for 12 weeks was shown to be similar to that of intravenous zoledronic acid 4mg every 4 weeks using biochemical markers of bone turnover to assess response (figure 1).[37] Both bisphosphonates similarly suppressed bone resorption, suggesting that they would have similar efficacy in preventing skeletal-related events.[37]

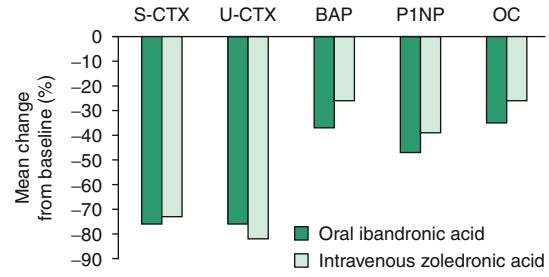

Fig. 1. Comparative efficacy of oral ibandronic acid and intravenous zoledronic acid on biochemical markers of bone turnover. Results of a randomised, open-label, parallel-group, multicentre study in patients with breast cancer and metastatic bone disease receiving oral ibandronic acid 50mg once daily (n = 128) or intravenous zoledronic acid 4mg every 4 weeks (n = 126) for 12 weeks.[37] Efficacy parameters consisted of serum and urinary levels of cross-linked C-terminal telopeptide of type I collagen (S-CTX and U-CTX), serum bone-specific alkaline phosphatase (BAP), serum amino-terminal procollagen propeptides of type I collagen (P1NP) and serum osteocalcin (OC).

5. Pharmacoeconomic Considerations

Two fully published cost-utility analyses, using the same economic model with essentially the same key assumptions, have estimated that treatment of breast cancer-derived bone metastases with oral ibandronic acid is dominant over treatment with either intravenous zoledronic acid or intravenous generic pamidronic acid.[40,41] One analysis was performed for patients receiving intravenous chemotherapy (4 months' duration) for their breast cancer,[40] while the other was for patients receiving oral hormonal therapy (7.5 months' duration).[41] Both analyses were conducted from the perspective of the UK National Health Service (NHS) and included only direct medical costs.

The model used clinical trial data where available or local expert opinion, and assumed a mean average survival for patients of 14.3 months, monthly hospital visits for intravenous bisphosphonate therapy, 3-monthly hospital visits for oral bisphosphonate therapy and equivalent therapeutic efficacy between ibandronic acid and zoledronic acid (both greater than pamidronic acid) based on the per-patient ratio of months spent with or without a skeletal-related event relative to placebo.[40,41] The model also assumed a greater reduction in analgesic use scores with ibandronic acid than the other bisphosphonates (7% vs 3%), a quality-of-life advantage for ibandronic acid over other bisphosphonates (0.02 increase in utility value), a lack of renal effects with ibandronic acid or pamidronic acid compared with zoledronic acid (0% vs 5% rate of renal impairment, plus a 0.015% probability of renal failure on zoledronic acid) and a higher premature treatment discontinuation rate for intravenous bisphosphonates (27–29%) than for oral ibandronic acid therapy (3%).[40,41] It was assumed that after 6 months of

bisphosphonate therapy, 25% of patients would decline further intravenous therapy and that one-half of these would switch to oral ibandronic acid, while the other half terminated all bisphosphonate therapy.[40,41] Both one-way and probabilistic sensitivity analyses were performed. Costs and effects were not discounted.[40,41]

In the analysis of patients receiving intravenous chemotherapy, treatment with oral ibandronic acid cost £386 less per patient than with intravenous zoledronic acid and £224 less per patient than with intravenous pamidronic acid (2003 values).[40] These total treatment costs included the costs of drug acquisition, managing renal impairment or failure, managing skeletal-related events and pain management. In addition, ibandronic acid added 0.019 quality-adjusted life-years (QALYs) [6.9 days] compared with zoledronic acid and 0.020 QALYs (7.2 days) compared with pamidronic acid. The base-case per-patient cost per QALY gained for oral ibandronic acid was £16 128 compared with £17 640 for zoledronic acid and £17 324 for pamidronic acid.[40] The model was robust to all one-way sensitivity analyses, with oral ibandronic acid remaining the dominant treatment option.[40]

Similarly, in the analysis of patients receiving oral hormonal therapy, treatment of bone metastases with oral ibandronic acid cost £307 less per patient than with intravenous zoledronic acid and £158 less per patient than with intravenous pamidronic acid (2003 values).[41] Ibandronic acid also added 0.018 QALYs (6.7 days) per patient compared with zoledronic acid and 0.019 QALYs (7.1 days) per patient compared with pamidronic acid. The base-case per-patient costs per QALY gained for ibandronic acid, zoledronic acid and pamidronic acid were £16 143, £17 447 and £17 157, respectively.[41]

In both analyses, sensitivity analyses indicated that the cost of managing skeletal-related events was the key cost driver in the model.[40,41] Per-patient drug acquisition costs for pamidronic acid would need to be reduced below £146 (chemotherapy analysis) or £152 (hormone therapy analysis) per month before ibandronic acid would stop being cost-saving.[40,41]

In contrast, preliminary data from two cost-utility analyses using a Markov model for hypothetical cohorts of patients with breast cancer and bone metastases estimated that oral ibandronic acid would be less cost effective than intravenous zoledronic acid and pamidronic acid from the perspective of the UK NHS[42] and would be less cost effective than intravenous zoledronic acid, intravenous pamidronic acid or oral clodronic acid from the perspective of the German outpatient.[43]

However, details of the model design and assumptions were limited, since the analyses were published as abstracts (plus posters from scientific meetings).[42,43] Importantly, these models assumed a higher efficacy for zoledronic acid than for the other bisphosphonates, based on skeletal-related event rate ratios derived from individual clinical trials for each agent, and equivalent efficacy for oral ibandronic acid and oral clodronic acid.[42,43]

In the analysis performed from the perspective of the UK NHS, intravenous zoledronic acid cost £1949 per patient less than oral ibandronic acid and £1160 less than intravenous generic pamidronic acid, while providing greater gains in discounted QALYs (0.822 vs 0.812 vs 0.816, respectively).[42] From the perspective of the German outpatient, the discounted cost per QALY gained compared with no treatment was lower for intravenous zoledronic acid (€14 394) than for intravenous pamidronic acid (€15 937), oral clodronic acid (€18 522), oral ibandronic acid (€22 753) or intravenous ibandronic acid (€24 386).[43]

A time-in-motion substudy of the randomised, open-label, multicentre clinical trial comparing oral ibandronic acid 50mg once daily with intravenous zoledronic acid 4mg every 3–4 weeks (section 4.2) assessed the time requirements at the week 8 clinic visit for a subset of patients (n = 36) at six selected clinics in Belgium, Switzerland, the UK and Russia.[44] Clinic visits for patients receiving zoledronic acid were 145 minutes longer than for patients receiving ibandronic acid at the Russian site and 85 minutes longer at the Western European sites. At the

Western European sites, zoledronic acid recipients (n = 13) required a mean of 181 minutes of personnel time (clinician, nurse, pharmacist or technician) per visit compared with 100 minutes per visit for ibandronic acid recipients (n = 15).[44]

6. Tolerability

Ibandronic acid was well tolerated in clinical trials. Most adverse events were related to disease progression and the overall incidence of adverse events with ibandronic acid was similar to that with placebo in controlled trials.[34,35,45] Treatment-related adverse events were usually of mild or moderate severity.[34,35,45] In the 2-year, phase III trials (section 4.1), the only notable adverse events that were considered possibly treatment-related and occurred with higher incidences than with placebo were flu-like syndrome, myalgia and diarrhoea with intravenous ibandronic acid 6mg and hypocalcaemia and upper gastrointestinal events (dyspepsia, nausea and oesophagitis) with oral ibandronic acid 50mg (figure 2).[46]

Very low incidences of treatment-related side effects with either intravenous or oral ibandronic acid were also observed during the 2-year open-label extensions of the original pivotal phase III trials.[47-49] The most common treatment-related event with intravenous ibandronic acid 6mg (n = 62) during the 2-year follow-up was gastroenteritis (n = 2),[49] while those with oral ibandronic acid 50mg (n = 115) were dyspepsia (n = 3), hypocalcaemia (n = 3) and oesophagitis (n = 2).[48]

There was no evidence of renal toxicity with ibandronic acid. In controlled trials, the incidences of renal adverse events with either intravenous ibandronic acid 6mg (4.0% vs 4.5%) or oral ibandronic acid 50mg (5.2% vs 4.7%) were similar to those with placebo.[46] Similarly, the incidence of elevated creatinine levels with oral ibandronic acid 50mg was similar to that with placebo (1.4% vs 2.2%). None of the renal events with ibandronic acid was graded as serious or resulted in treatment discontinuation.[46] Specific assessment of multiple biochemical markers of kidney function in a subset of patients (n = 74) participating in the pivotal phase III trial of intravenous ibandronic acid failed to detect any evidence of renal impairment; proteinuria, haematuria, enzymuria and serum creatinine did not differ significantly from baseline or placebo.[50] Likewise, neither intravenous nor oral ibandronic acid produced any significant renal toxicity during the 2-year extension studies.[48,49]

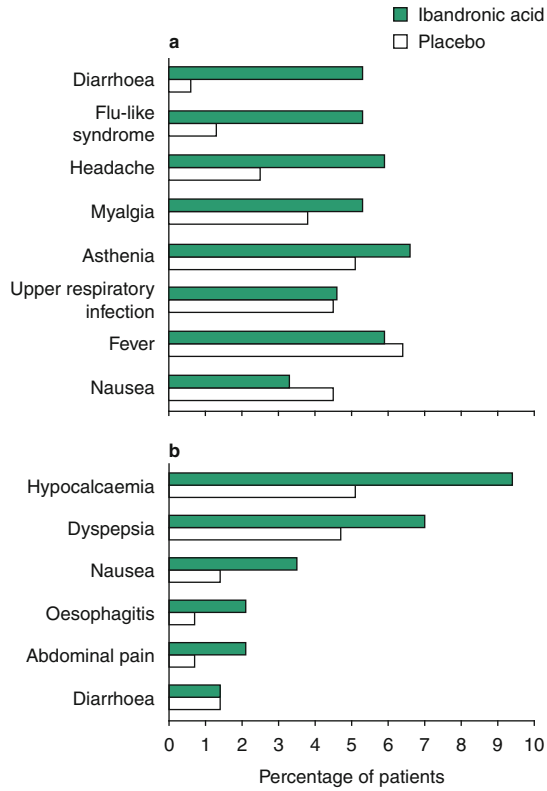

Fig. 2. Tolerability profile of ibandronic acid in patients with bone metastases of breast cancer. Most common treatment-related adverse events reported in patients treated with (**a**) intravenous ibandronic acid 6mg every 3–4 weeks (n = 152) for 96 weeks or (**b**) oral ibandronic acid 50mg once daily (n = 286) for 96 weeks in randomised, double-blind, placebo-controlled, phase III clinical trials.[46]

Osteonecrosis of the jaw is a rare, serious adverse event associated with the use of bisphosphonates. Several instances of osteonecrosis of the jaw have been reported in association with the use of intravenous (n = 5) or oral (n = 2) ibandronic acid, although four patients (including both patients receiving oral

ibandronic acid) had a prior history of treatment with other bisphosphonates.[51]

In the head-to-head comparative trial, the overall incidence of adverse events throughout the 12-week study was numerically higher with intravenous zoledronic acid 4mg than oral ibandronic acid 50mg (76% vs 65%), although no information was provided regarding statistical analyses since the study was published as an abstract.[52] The difference was greatest in the first 3 days of the study (47% vs 8%), with the events consisting predominantly of acute-phase reactions (pyrexia, chills, flu-like syndrome, arthralgia and myalgia).[52] Patients receiving zoledronic acid experienced apparently higher incidences of bone pain (21% vs 12%), serious adverse events (8% vs 6%) and treatment withdrawals (5% vs 3%) than ibandronic acid recipients, but a lower incidence of gastrointestinal events (18% vs 23%).[52]

7. Dosage and Administration

Ibandronic acid is approved in the EU for the prevention of skeletal-related events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.[7] Ibandronic acid may be administered intravenously (6mg infused over 1 hour every 3–4 weeks) or orally (50mg once daily in the morning after an overnight fast and 30 minutes prior to eating or drinking other than plain water).[30] In patients with severe renal impairment (creatinine clearance <30 mL/min), the oral dosage should be reduced to 50mg once weekly and the intravenous dosage to 2mg infused over 1 hour every 3–4 weeks.[30]

In addition to the aforementioned indication discussed in this review, intravenous ibandronic acid (2–4mg infused over 2 hours) is also approved in the EU for the treatment of tumour-induced hypercalcaemia with or without metastases[30] and oral ibandronic acid (2.5mg once daily or 150mg once monthly) is approved in the US for the treatment and prevention of osteoporosis in postmenopausal women.[53]

8. Place of Ibandronic Acid in the Prevention of Skeletal-Related Events in Metastatic Breast Cancer

A high proportion of patients with metastatic breast cancer develop bone metastases and as a consequence experience considerable pain and disability from the resultant complications, which include pathological fractures, hypercalcaemia and spinal cord compression.[11] While not appropriate for all patients,[4,54] bisphosphonates have proven to be effective in preventing the skeletal complications of metastatic bone disease.[1,5,55] They provide significant analgesia within weeks of beginning therapy, significant reductions in the need for radiotherapy within 6 months and significant reductions in the need for orthopaedic surgery within 2 years.[1,55] Clinical benefit from bisphosphonate therapy appears to correlate with improvements in the rate of bone resorption.[2] However, there is no survival advantage in treating bone metastases with bisphosphonates.[1,55] Bisphosphonates are most appropriate in patients with metastases only in the bone, since the survival of patients who also have soft-tissue metastases is generally insufficient to gain the full benefits of therapy.[4,54] Although still conjectural and the subject of investigation, it is thought that pretreatment of patients before bone metastases develop (adjuvant therapy) would be most effective, since it would actually decrease the incidence of bone metastases and might enhance survival.[1] The benefits of bisphosphonates appear to cease upon discontinuation of therapy, suggesting that therapy should be life-long.[55] What modifications to bisphosphonate regimens might be necessary when skeletal-related events occur during therapy remain to be determined.[54,55]

Bisphosphonates preferentially bind to bone at sites of active remodelling, are released from the bone matrix during bone resorption and are taken up by osteoclasts.[2] They inhibit osteoclast activity and survival, resulting in a marked reduction in osteoclast-mediated bone resorption. They may have direct inhibitory effects on breast cancer cells, preventing the adhesion of tumour cells and inducing tumour cell apoptosis.[25,56] Newer-generation,

aminobisphosphonates are considerably more potent than first generation agents. They are active at micromolar concentrations and can be administered in smaller doses. Of the available bisphosphonates, only zoledronic acid is more potent than ibandronic acid, although potency does not necessarily relate to clinical efficacy.

In *in vitro* or animal models of breast cancer bone metastases, ibandronic acid not only inhibited bone resorption by osteoclasts and induced apoptosis of osteoclasts at osteolytic lesions, but also inhibited tumour cell adhesion and invasion, induced tumour cell apoptosis and reduced the tumour burden in bone (section 2.2). Ibandronic acid and anticancer agents provided additive effects with respect to reducing the incidence of metastases to bone and other tissues.

Ibandronic acid is available in both an intravenous and an oral formulation. Intravenous formulations generally require only once-monthly administration, can be administered at the same time as anticancer therapy and ensure absolute compliance, but are costly, possibly inconvenient to patients and place additional demands on usually over-committed intravenous therapy services. In contrast, daily oral therapy is more convenient and less costly to administer, but does not guarantee compliance. Clodronic acid is the only other bisphosphonate approved for the treatment of bone metastases in patients with breast cancer that is available in an oral formulation. Although widely used, it has a low oral bioavailability and requires the administration of large daily oral doses of 1.6–3.2g in multiple tablets that can be a barrier to compliance with some patients. The much higher relative potency of ibandronic acid means that it can be administered as a single daily 50mg tablet and is, therefore, less of a barrier to good compliance. Since oral bisphosphonates need to be taken on an empty stomach, upper gastrointestinal adverse events may reduce compliance in some patients, while failure to maintain adequate pre- and post-dose fasting periods may markedly reduce the drug's efficacy.

In randomised, double-blind trials in patients with breast cancer and bone metastases, intravenous ibandronic acid 6mg and oral ibandronic acid 50mg displayed similar therapeutic efficacy. Intravenous ibandronic acid significantly reduced the overall SMPR by 20% compared with placebo over 2 years, while oral ibandronic acid similarly reduced the overall SMPR by 18% compared with placebo over two years (section 4.1). Oral ibandronic acid 50mg produced a significant 39% reduction in the risk of skeletal-related events, which was similar to the 40% reduction observed with intravenous ibandronic acid 6mg.

Both intravenous ibandronic acid 6mg and oral ibandronic acid 50mg significantly improved patients' health-related quality of life in the pivotal clinical trials, although there were minor differences between the formulations in the functional quality-of-life domains that were most responsive to therapy (section 4.1.3).

In the only head-to-head active comparison performed to-date, oral ibandronic acid 50mg once daily was shown to be similar in efficacy to intravenous zoledronic acid 4mg every 4 weeks when administered for 12 weeks to patients with breast cancer and bone metastases (section 4.2). However, the study used surrogate endpoints (biochemical markers of bone turnover) as appropriate for the study duration, since significant reductions in all types of clinical skeletal-related events would not likely be apparent within such a short treatment duration. Although the bone turnover markers are considered to accurately reflect bone resorption and correlate with clinical response, there is no finite quantitative correlation with clinically manifested skeletal-related events.

Thus, preliminary evidence suggests that oral ibandronic acid is likely similar in efficacy to intravenous zoledronic acid, which in turn has been shown to be as effective as intravenous pamidronic acid in the prevention of skeletal-related events in breast cancer patients with bone metastases.[57] However, comparative clinical trials of sufficient size and duration using relevant clinical endpoints are necessary to unequivocally define the relative clinical efficacies of the available bisphosphonates.

Ibandronic acid was generally well tolerated in clinical trials and their long-term extensions. Adverse events were infrequent and mostly of mild or moderate severity. They commonly consisted of flu-like syndrome, diarrhoea, headache, asthenia and myalgia in patients receiving intravenous ibandronic acid therapy and hypocalcaemia plus upper gastrointestinal symptoms in patients receiving oral ibandronic acid therapy (section 6).

Unlike some other bisphosphonates, such as zoledronic acid, ibandronic acid does not appear to have any potential for producing renal toxicity, either as a result of long-term cumulative nephrotoxicity or following rapid infusion. Evidence suggests that it should be possible to administer ibandronic acid by rapid intravenous infusion over 15 minutes without any risk of adverse renal effects and therefore without the need for the monitoring of renal function.[58]

The absence of renal toxicity associated with ibandronic acid and the agent's proven ability to reduce bone pain have led to investigations of the effect of short-term intensive treatment in providing more rapid pain relief.[59] Preliminary evidence indicates that intensive loading doses of intravenous ibandronic acid (e.g. 4mg daily for 4 consecutive days) can produce significant ($p < 0.001$) reductions in bone pain scores within 7 days.[59,60] The reduction in pain scores was sustained for at least 6 weeks and was achieved without compromising renal safety.[60] Similarly, intravenous ibandronic acid 6mg daily for 3 consecutive days in patients with painful osseous metastases resulted in significant reductions from baseline in mean pain scores on day 3 (2.5 vs 6.8; $p < 0.001$), with 83% of patients having significant improvement in bone pain on day 2.[61] No renal adverse events were reported. Studies assessing the rapid relief of metastatic bone pain with loading doses of ibandronic acid are ongoing.

The treatment of skeletal-related events resulting from bone metastases in breast cancer patients incurs significant costs within the healthcare system, which have been estimated at $US14 580 per patient (for either a 12- or 15-month period).[62] However, the costs of bisphosphonate therapy to prevent skeletal-related events are also very high. Previous estimates of the incremental cost-effectiveness ratio versus placebo for intravenous pamidronic acid have ranged from approximately $Can18 700 per QALY gained[63] to $US108 200 per QALY gained for patients receiving chemotherapy for cancer[64] or $US305 300 per QALY gained for patients receiving hormonal anticancer therapy.[64]

The incremental cost-utility ratio for oral ibandronic acid in the treatment of bone metastases of breast cancer versus no treatment was estimated in the German analysis at €22 753 per QALY gained, which was considered to be cost effective on the assumption that €30 000 would be the maximum that society would be prepared to pay for a QALY gained.[43] Similarly, the base-case cost-utility ratios for oral ibandronic acid in the fully published UK analyses (£16 128 and £16 143 per QALY gained) were considered cost effective relative to a threshold of £30 000.[40,41]

The cost effectiveness of oral ibandronic acid relative to other bisphosphonates in the treatment of bone metastases in breast cancer patients is not entirely clear. Fully published cost-utility analyses suggest greater cost effectiveness for oral ibandronic acid than for zoledronic acid and pamidronic acid, whereas preliminary data from recent cost-utility analyses, available only as abstracts, do not. The two sets of analyses use quite different assumptions regarding relative therapeutic efficacy, treatment discontinuation rates, adverse event rates and quality-of-life benefits (see section 5). A definitive analysis of the relative cost effectiveness of the bisphosphonates will not be possible until appropriate comparative studies are performed to provide the relative data values necessary for accurate modelling.

In conclusion, ibandronic acid is a potent bisphosphonate, which effectively inhibits osteoclast-mediated bone resorption. In clinical trials, the intravenous and oral formulations were equally effective in preventing skeletal-related events and improving quality of life in patients with bone metastases of breast cancer. Both intravenous and oral ibandronic acid reduced metastatic bone pain scores below baseline levels for up to 2 years. Oral iban-

dronic acid is administered as a single 50mg tablet taken once daily. It suppressed bone resorption in breast cancer patients with bone metastases to an extent similar to that observed with intravenous zoledronic acid. Both intravenous and oral ibandronic acid were well tolerated with no evidence of renal toxicity. Ibandronic acid is therefore a valuable addition to the bisphosphonates used in the treatment of bone metastases of breast cancer, offering high potency and the convenience of oral administration, combined with the absence of renal toxicity.

Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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