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Ibandronate in the Management of Postmenopausal Osteoporosis

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Abstract: Oral daily and weekly bisphosphonates were considered, for several years, as the mainstay for the treatment of postmenopausal osteoporosis. However, the inconvenience of frequent dosing is known to negatively affect adherence to therapy in the long-term, hence outcomes. This has prompted the development of convenient oral bisphosphonate regimens that feature simple, less frequent dosing schedules. Ibandronate is a potent, nitrogen-containing bisphosphonate which, uniquely, can be administered either orally, monthly, or as an intravenous injection, every 3 months. A positive impact for adherence has been observed with a reduction in the bisphosphonate dosing frequency. Anti-fracture efficacy of the various currently available regimens of ibandronate is documented in randomized controlled clinical trials, non-inferiority studies, meta-analyses and real-life settings studies. The present paper summarizes the pharmacology, efficacy and tolerability of oral and intravenous ibandronate, when administered with extended dosing intervals, in postmenopausal osteoporosis.

Keywords: bisphosphonate, osteoporosis, treatment, ibandronate, fracture, adherence

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Introduction

Postmenopausal osteoporosis may develop in women following either naturally-occurring or surgically-induced menopause. Osteoporosis is characterized by low bone mass and microarchitectural deterioration, leading to compromised bone strength and an increase in the risk of fracture. Osteoporosis is clinically diagnosed as an history of fragility fracture and may also be diagnosed by a report of low bone mineral density (BMD), after dual-energy x-ray absorptiometry (DXA) scanning. DXA measures areal BMD is influenced by bone mass as well as the degree of mineralization of the bone matrix. DXA does not specifically measure bone microarchitecture or distinguish between the trabecular and cortical components of bone. Recently, clinical risk factors were shown to be significantly associated with the risk of hip and other osteoporotic fractures, independently of BMD measurement. The combination of clinical risk factors and BMD provides higher specificity and sensitivity than either alone, for fracture risk assessment. These results provide the basis for the integrated use of validated clinical risk factors, in men and women, to improve fracture risk prediction.¹ Recently developed non-invasive imaging techniques, such as computed tomography and magnetic resonance imaging, can be used to quantitatively assess micro- and macro-structure and, therefore, provide a more detailed report on the condition of the bone.^{2,3} However, due to cost and availability, these advanced techniques are not used in routine clinical practice.

Although routine DXA screening in women aged at least 65 years or postmenopausal women younger than 65 years with associated risk factors is recommended, osteoporosis is often not diagnosed until the patient suffers a fragility fracture. Osteoporosis is a risk factor for fracture just as hypertension is for stroke. The most common fractures are those of the vertebrae, proximal femur and distal forearm. Fractures of the vertebrae and proximal femur may lead to chronic pain, disability and death. Within the first year post-hip fracture, 80% of patients are unable to carry out at least one independent activity of daily living and the associated mortality rate is 20%.⁴ Vertebral fractures also cause significant complications including back pain, height loss, kyphosis and death. These physical manifestations of osteoporosis can lead to

psychological symptoms, most notably depression and loss of self-esteem.

Therefore, postmenopausal osteoporosis is a silent, chronic disease with serious consequences if not diagnosed and treated effectively. The socio-economic impact of this disease will continue to grow with the globally-increasing elderly population. It is estimated that 1 in 3 women over 50 will experience osteoporotic fractures and by 2050, the worldwide incidence of hip fracture in women is projected to increase by 240%.^{5,6} In the US, costs associated with osteoporotic fractures were estimated to be \$17 billion in 2005, increasing by up to 50% by 2025.⁷ The direct costs associated with osteoporotic fractures in Europe were estimated to be €31.7 billion in 2000 and are expected to increase to €76.7 billion in 2050.⁸

Included within the above costs are acute fracture care (hospitalization, surgery, joint prostheses, etc.), chronic fracture care (rehabilitation) and therapeutic options for the treatment of postmenopausal osteoporosis, which include calcium and vitamin D, strontium ranelate, selective estrogen-receptor modulators, calcitonin, teriparatide and bisphosphonates.⁹

The nitrogen-containing bisphosphonates, available for oral and intravenous (i.v.) administration, are one of the current drugs of choice. Ibandronate (Bonviva®) is a nitrogen-containing bisphosphonate, available in the US and EU since 2005 for monthly oral dosing and by quarterly i.v. injection since 2006.^{10,11}

Mechanism of Action, Metabolism and Pharmacokinetic Profile

The molecular structure of all bisphosphonates includes a P-C-P (Phosphorous-Carbon-Phosphorous) backbone; the bone mineral affinity and antiresorptive potency is derived from the chemical moieties at the R1 and R2 positions (R = residues at C). Ibandronate (3-[N-methyl-N-pentyl] amino-1-hydroxypropane-1, 1-diphosphonic acid, monosodium salt, monohydrate; molecular weight 359.24) has one of the most potent structural arrangements, with a hydroxyl group at the R1 position enhancing affinity for bone and a tertiary nitrogen group at the R2 position that significantly increases potency compared with the non-nitrogen-containing bisphosphonates (e.g. etidronate, clodronate).¹² All nitrogen-containing bisphosphonates work by inhibiting farnesyldiphosphate synthase. The rank order of potency for in vitro inhibition is: alendronate,



ibandronate, risedronate and zoledronate.¹³ The rank order of potency of *in vivo* inhibition of bone resorption in rates is: alendronate, risedronate, ibandronate and zoledronate.^{13–16}

The pharmacokinetic profile of ibandronate has previously been described in detail by Barrett and colleagues.¹⁷ Therefore, presented here is an overview of the key points.

Consistent with other oral bisphosphonates, oral ibandronate (pKa 2.0, 6.3 and 10.5) is poorly absorbed from the gastrointestinal (GI) tract. Oral bioavailability is estimated to be 0.63%. It is likely that poor absorption of oral bisphosphonates is due to their negative charge at physiological pH. Paracellular transport is considered to be the most likely route of absorption, as transcellular transport through the epithelial membrane is reduced due to the polarity. Pharmacokinetics following oral administration show both inter- and intra-subject variability (area under curve [AUC]: >70%; coefficient of variation: ~46%). Nevertheless, oral ibandronate is quickly absorbed, mean peak plasma concentrations (C_{\max}) are achieved by approximately 1 hour.

Similar to the oral administration of other bisphosphonates, to maximize bioavailability ibandronate should be taken after an overnight fast of at least 6 hours and 60 minutes before the first food or drink (other than water) of the day. Plasma concentrations of ibandronate are noticeably reduced when taken immediately following food (90%: AUC_{0–∞} ratio: 11%; 90% CI = –9%, –32%).¹⁷

Following absorption and initial systemic exposure, 40%–50% of ibandronate is distributed and bound to bone, the remainder is excreted unchanged in the urine. The volume of distribution (VD) for ibandronate administered intravenously is 90–368 L in healthy subjects and 103 L in postmenopausal women with osteopenia. This high VD reflects the distribution of ibandronate into bone throughout the body. In rats, receiving daily subcutaneous injections of ibandronate in doses ranging from 0.003 to 0.3 mg/kg/day for 9 days, concentration of ibandronate increased dose-dependently in mandible, femur and lumbar vertebrae, with similar concentration per bone at each dose level, ranging from values below quantification limit (low dose) up to approximately 10 ng ibandronate/mg bone dry weight (high dose). There was a relatively similar bisphosphonate uptake

between the femur and lumbar vertebrae bones, whereas the uptake in the jaw was statistically smaller with regard to the absolute values, suggesting no preferential bisphosphonate uptake in the jaw.¹⁸

Ibandronate is not metabolised. No metabolites were produced when ibandronate was incubated *in vitro* with rat, dog and human liver microsomes or when oral or *i.v.* ibandronate was administered to humans or animals.¹⁷ Even at concentrations greater than 1000-fold than those found clinically, there is a lack of affinity between ibandronate and the major cytochrome P450 isoforms. Metabolic stability and urinary excretion of the unchanged compound are characteristics associated with all bisphosphonates.

Within 24 hours, unabsorbed oral ibandronate is excreted in the faeces and ~50%–60% of *i.v.* ibandronate is excreted unchanged in the urine, absorbed oral ibandronate is also excreted unchanged in the urine. However, the half-life of ibandronate is multiphasic, following initial elimination in the first 24 hours, the elimination half-life ($t_{1/2}$) of ibandronate is 10–60 hours due to elimination from the bone and subsequent elimination from the kidney. The calculated renal clearance (CLR) of ibandronate is 54–112 mL/min (in healthy postmenopausal women), which accounts for 50%–60% of the total clearance, with the remainder distributed into bone. Over the following years ibandronate is released from the bone and excreted renally. Thus, the CLR of ibandronate, and other bisphosphonates, is dependent on renal function, resulting in CLR being reduced in renally impaired patients.

It is acknowledged that all patients receiving multiple medications, such as those with postmenopausal osteoporosis, are potentially at risk for drug-drug interactions. However, ibandronate does not inhibit or alter cytochrome P450 (CYP) metabolism, as previously discussed. Therefore, pharmacokinetic studies have shown that ibandronate does not interact with tamoxifen, melphalan or prednisolone. A minor increase (20%) in the AUC of ibandronate in combination with ranitidine has been noted, although this was attributable to an increase in gastric pH and was not considered to be clinically relevant.

The efficacy of intermittent administration of subcutaneous and intravenous ibandronate has been demonstrated in various animal models (rat, dog, minipig and monkey). In these animals, ibandronate



administered subcutaneously or intravenously, with extended intervals between doses reduces bone turnover, increases bone mineral density and maintains bone quality in a dose-dependent manner. Furthermore, studies in rats and dogs compared in continuous and intermittent treatments schedules indicate similar efficacy when the same cumulative dose is applied over the duration of the study. These studies with ibandronate illustrate the concept that the total cumulative dose of bisphosphonate administered determines the response, independent of whether the dose is given daily or less frequently in a given time period. Important factors for determining efficacy and the magnitude of response are the doses given, the length of the interval between doses and the underlying bone turnover rate.¹⁹

The pharmacodynamics of bisphosphonates, in human, are measured by assessment of BMD and bone turnover markers. In a study of postmenopausal osteopenic women ($n = 180$), daily oral ibandronate 0.25–5 mg increased BMD of the spine and proximal femur and reduced bone turnover markers (osteocalcin and urinary c-telopeptide of type 1 collagen [CTX]) versus placebo.²⁰ The 2.5 mg daily dose was considered to be the most effective. Monthly oral ibandronate (50–150 mg), given to postmenopausal women with osteoporosis ($n = 144$), substantially reduced serum and urinary CTX from baseline by day 91 (30 days after the final dose; $p < 0.001$ for the 100 mg and 150 mg doses versus placebo).²¹ The data showed highly significant associations between pharmacokinetic parameters of ibandronate and the clinical response in bone mass and bone turnover.²² The change from baseline in serum and urinary CTX in the area under the effect curve (day 1–91) indicated a dose-response relationship. A dose-ranging study of ibandronate 0.25–2 mg administered every 3 months by i.v. injection ($n = 126$) reported increases in BMD of the spine and proximal femur and reduced bone turnover markers (osteocalcin and CTX) in a dose-dependent manner versus placebo.²³ A study of healthy postmenopausal women ($n = 73$) receiving i.v. ibandronate (1 mg or 2 mg) or no treatment assessed the levels of serum CTX and osteocalcin at 19 consecutive time points.²⁴ A rapid onset of treatment effect was reported with the nadir for serum CTX reached 7 days after drug administration. At 2 weeks after drug administration, the serum levels of CTX had started to rise, reaching –16% and –20% immediately

before the second drug administration (Day 84). Osteocalcin decreased more slowly reaching a nadir after 5 months. Considering these data alongside that reported for other studies discussed later, it appears that maintaining bone turnover reduction within the premenopausal range is important for anti-fracture efficacy rather than reported fluctuations during treatment.

With the aim of identifying practical dosing regimens for further clinical study, an extensive modelling and simulation project was completed with ibandronate.^{25,26} A simplified kinetic-pharmacodynamic (K-PD) model, developed from a 4-compartment pharmacokinetic-pharmacodynamic model, was designed to accurately predict the pharmacodynamic response, excretion of urinary CTX, following administration of varying doses of ibandronate. The model included an allowance for the effects of supplemental calcium therapy and allowed simultaneous fitting of i.v. and oral ibandronate data. The residual (i.e. 1 month after dosing) level of median decrease in urinary CTX following administration of several different once-monthly oral ibandronate doses over 12 months was assessed using the K-PD model. Simulations from the 100 virtual trials, which each included 250 virtual patients, demonstrated substantial reductions in the median residual levels of urinary CTX with 100 mg and 150 mg monthly oral ibandronate at 3, 6, 9 and 12 months. The efficacy and safety of these two monthly ibandronate doses were then assessed in clinical trials.

Clinical Studies

Monthly oral ibandronate (150 mg) and quarterly i.v. injection ibandronate (3 mg) are the regimens used in clinical practice for the treatment of postmenopausal osteoporosis.^{10,11} Although daily oral ibandronate (2.5 mg) has also received a favourable response from the regulatory authorities, this regimen is not available for prescription.

Oral and i.v. ibandronate have been studied extensively for prevention and treatment of postmenopausal osteoporosis. The key efficacy studies are detailed below.

Oral ibandronate

Oral daily ibandronate (2.5 mg) was investigated for the prevention of bone loss in postmenopausal



women without osteoporosis. BMD at the lumbar spine and hip were significantly increased (3.1% and 1.8%, respectively; $p < 0.0001$ versus placebo) after 24 months.²⁷ In ambulatory postmenopausal women, aged 45–60 years, with baseline lumbar spine BMD T-score < -1.0 and > -2.5 and baseline T-score > -2.5 at the total hip, trochanter and femoral neck, and no prior vertebral or low-trauma osteoporotic fractures at baseline, monthly oral ibandronate (150 mg) induced larger increases in lumbar spine BMD after 1 year compared with subjects receiving placebo (3.7% vs. -0.4%; $p < 0.0001$). After 3 months, median serum C-terminal telopeptide of type I collagen levels were reduced by $>55\%$ in the ibandronate group compared with 4% in the placebo group. At 1 year, 88.2% of the participants treated with ibandronate achieved increases in lumbar spine BMD $> 0\%$ compared with 38.6% of subjects receiving placebo.²⁸ Treatment regimens were well tolerated in both the ibandronate treated and placebo groups suggesting that monthly ibandronate therapy is an appropriate option to prevent bone loss in postmenopausal women with low bone mass.

The anti-fracture efficacy of daily oral ibandronate (2.5 mg) and intermittent oral ibandronate (20 mg every other day for 12 doses every 3 months) was assessed in postmenopausal osteoporotic women in the iBandronate Osteoporosis trial in North America and Europe (BONE).²⁹ The two ibandronate regimens were associated with significant reductions in the risk of vertebral fractures versus placebo (62%, $p = 0.0001$ and 50%, $p = 0.0006$, respectively). BONE was the first study to demonstrate an anti-fracture effect with an intermittently administered bisphosphonate. A significant reduction in non-vertebral fractures was not seen in the overall population (mean total hip BMD T-score -1.7). However, subgroup analyses including women at higher risk for fracture showed significant reductions in non-vertebral fracture risk (femoral neck BMD T-score < -3.0 : 69%, $p = 0.012$; lumbar spine BMD T-score < -2.5 and a history of clinical fractures in the past 5 years: 62%, $p = 0.025$).^{29,30} Retrospective analysis from the BONE study demonstrated that, in addition to being effective in significantly reducing the risk of new vertebral fractures of all severities, oral daily ibandronate has a pronounced effect on the more severe, most clinically relevant, vertebral fractures: a significant and sustained reduction of

59% in the relative risk of combined new moderate and severe vertebral fractures was observed at years 1 ($P = 0.0164$), 2 ($P = 0.0004$), and 3 ($P < 0.0001$).³¹

Following the demonstration of anti-fracture efficacy with daily ibandronate the focus became extending the dose-free interval to develop a more convenient regimen. As identified through modelling and simulation, previously discussed, 50 + 50 mg (single doses on consecutive days), 100 mg and 150 mg doses of monthly ibandronate were studied in the Monthly Oral iBandronate In LadiEs (MOBILE) study.^{32,33} The 150 mg dose produced the greatest gains in BMD versus daily ibandronate (2.5 mg) at 2 years (lumbar spine BMD: 6.6% versus 5.0%, respectively, $p < 0.001$). All regimens reduced serum CTX to within the premenopausal range by 3 months and maintained the lower levels throughout the 2-year study. A 3-year long-term extension (LTE) to MOBILE is currently ongoing. An interim analysis at 1 year (3 years on treatment) has shown that patients receiving continuous monthly ibandronate (100 mg or 150 mg) in the MOBILE LTE continued to gain lumbar spine BMD and at the hip.³⁴ The reduced levels of serum CTX reported during MOBILE have been maintained in the LTE.

In addition to the above studies focusing solely on ibandronate, the efficacy of monthly oral ibandronate has been compared with weekly alendronate with regards to BMD gains at the lumbar spine and total hip (primary endpoint; MOTION study).³⁵ Based on the pre-specified criteria, non-inferiority of both regimens was reported at 1 year for changes in BMD (lumbar spine: 5.1% and 5.8%, respectively; total hip: 2.9% and 3.0%, respectively). Increases in trochanter and femoral neck BMD were also similar with both regimens. Although the reduction in bone markers was faster with ibandronate, changes in both serum CTX and amino-terminal propeptide of type I procollagen (P1 NP) were similar in the two treatment arms.³⁶ The AUC values (%*days) for serum CTX were -27,595.7 for ibandronate and -27,924.2 for alendronate, and for P1 NP, -20,057.9 for ibandronate and -20,193.2 alendronate.

Intravenous ibandronate

A randomized anti-fracture efficacy study of i.v. ibandronate injections, 1 mg and 0.5 mg once every 3 months, was conducted at a similar time to



BONE.³⁷ Although an almost significant trend toward a reduction in the incidence of fracture was observed with ibandronate compared with placebo, the magnitude of fracture reduction did not reach statistical significance. However, ibandronate produced dose-dependent increases in lumbar spine BMD and decreases in biochemical bone markers relative to placebo. It was, also shown, that a 2 mg ibandronate i.v. regimen provides significantly greater BMD increases and significantly greater suppression of bone resorption markers than the 1 mg dose used in the fracture prevention study,^{23,38,39} with no significant difference in the overall number of adverse event in the ibandronate group compared with the placebo group. Therefore, it was determined that either higher doses of intermittent ibandronate or a shorter dose-free interval would be required to achieve fracture protection.

To evaluate this hypothesis, the Dosing IntraVenous Administration (DIVA) study assessed the efficacy of 2 mg every 2 months and 3 mg quarterly ibandronate i.v. injections compared with daily oral ibandronate (2.5 mg).^{40,41} The design of DIVA was the same as MOBILE, with the exception of the different route of ibandronate administration. At 2 years, both i.v. regimens produced improvements in spinal BMD that were superior to oral ibandronate (2.5 mg; $p < 0.001$). In addition, BMD gains at all hip sites were greater in the i.v. arms than the oral arm. Serum CTX levels were markedly reduced in all arms. As with the oral ibandronate, MOBILE study, a 3-year LTE of DIVA is ongoing.⁴² In the LTE, patients received ibandronate i.v. injections 2 mg every 2 months and 3 mg quarterly only. Therefore, patients who were previously receiving oral ibandronate have been reallocated to an i.v. regimen. In the overall study population, further BMD increases were seen at the lumbar spine and at the hip (interim data at 1 year, 3 years on treatment). In addition, a pooled analysis evaluating only those patients who remained on the same i.v. treatment for 3 years showed significant gains in lumbar spine and total hip BMD versus baseline ($p < 0.0001$). The reduction of serum CTX seen in the 2 years of DIVA was maintained in the first year of the LTE.

Safety

As with any treatment, the benefits must be considered alongside the potential side effects that may be experienced

by the patient. This is particularly true when considering a long-term therapy for a chronic disease, such as osteoporosis.

Oral and i.v. ibandronate have been studied at various doses and with varying dose-free intervals. These regimens have been collectively reviewed to obtain an overall safety and tolerability profile. Oral (0.25–5 mg daily and 50–150 mg monthly) and i.v. (2 mg every 2 months and 0.25–3 mg quarterly) ibandronate have demonstrated similar overall tolerability profiles to placebo, with a comparable number of reported adverse events.^{20,21,23,29} Although not compared directly with placebo, the overall tolerability profiles for monthly oral ibandronate (150 mg) and quarterly i.v. ibandronate (3 mg), the licensed regimens, are similar to daily oral ibandronate (2.5 mg; Table 1).^{32,33,40,41}

In clinical practice, orally administered bisphosphonates have previously been associated with GI intolerance. In the BONE study, the overall incidence of GI adverse events was similar with ibandronate (daily or intermittent) and placebo.⁴³ This was also true when GI adverse events reported by patients with a history of upper GI disorders or patients taking concomitant non-steroidal anti-inflammatory drugs (NSAIDs) were reviewed. Importantly, the incidence of GI adverse events in the overall MOBILE study population, and those patients taking NSAIDs, was similar with monthly and daily oral ibandronate.³³

In some patients, i.v. administration of nitrogen-containing bisphosphonates is associated with a flu-like illness in the period immediately after dosing;^{44–47} although less frequently, similar symptoms have also been observed with oral bisphosphonates. Therefore, as would be expected, patients receiving monthly oral or quarterly i.v. ibandronate in clinical trials have reported a slightly higher incidence of flu-like illness (including the investigator-reported event terms ‘influenza-like illness’ and ‘acute-phase reaction’) compared with the daily oral regimen.^{33,41} However, these symptoms are generally mild to moderate in severity, occur within 3 days of the first dose and resolve without treatment, within 7 days.

Renal issues are also commonly associated with bisphosphonate i.v. infusion administration and such issues have led to the infusion times of some bisphosphonates being extended. Interestingly, a pooled

**Table 1.** Summary of adverse event data at 2 years with monthly oral ibandronate 150 mg and quarterly i.v. ibandronate 3 mg compared with daily oral ibandronate 2.5 mg (%; safety populations).^{24,32}

	Mobile		Diva	
	2.5 mg daily (n = 395)	150 mg monthly (n = 396)	2.5 mg daily (n = 465)	3 mg quarterly (n = 469)
Any AE	76.5	80.1	87.7	85.3
Any drug-related AE	32.4	36.9	36.8	42.0
Leading to withdrawal	7.6	6.8	6.0	6.5
Any serious AE	9.6	11.4	14.4	13.2
Any serious drug-related AE	0.5	0.3	0.9	0.4
Leading to withdrawal	0.3	0.3	0.4	0

Abbreviation: AE, adverse event.

safety database including 3,295 patients receiving i.v. ibandronate injection 2–12 mg annually found no cases of acute renal failure and no adverse effects on indicators of renal toxicity or function.⁴⁸ Mean CLR in patients receiving i.v. ibandronate remained stable compared with baseline and was similar to that seen in patients receiving oral ibandronate or placebo. Marked changes in serum creatinine occurred in only a small number of patients, with no dose-response evident. Although it has been reported in pharmacokinetic studies that the CLR of ibandronate in renally impaired patients is lower than in normal subjects,¹⁷ no dose adjustment is necessary for patients with mild or moderate renal impairment where CLR is ≥ 30 mL/min.^{10,11} Ibandronate is not recommended for patients with a CLR < 30 mL/min due to limited clinical experience. In addition, no adjustment of ibandronate dose is required for the elderly or patients with hepatic impairment.^{10,11}

Older patients (≥ 70 years) receiving oral daily and intermittent ibandronate are at no greater risk of adverse events than older patients receiving placebo. Older patients are at no greater risk of upper GI adverse events than younger patients or patients receiving placebo.⁴⁹

A potential side effect associated with bisphosphonates is osteonecrosis of the jaw (ONJ). The incidence of ONJ in the general population is unknown; this rare condition also may occur in patients not receiving bisphosphonates. Case reports have discussed ONJ development in patients with multiple myeloma or metastatic breast cancer receiving bisphosphonates as palliation for bone metastasis. These patients are also receiving chemotherapeutic

agents that might impair the immune system and affect angiogenesis. The incidence or prevalence of ONJ in patients taking bisphosphonates for osteoporosis seems to be very rare (1/100000 patients-years). No causative relationship has been unequivocally demonstrated between ONJ and bisphosphonates therapy, including ibandronate. A majority of ONJ occurs after tooth extraction. Furthermore, the underlying risk of developing ONJ may be increased in osteoporotic patients by comorbid diseases.⁵⁰

Owing to the reported incidence of rhabdomyolysis, defined as the combination of muscle pain and creatine kinase (CK) elevation >10 times the upper limit of normal, associated with statin therapy and following the publication of the CK monitoring recommendations,⁵¹ an exploratory study was conducted to characterise the CK profile in postmenopausal women treated with ibandronate [Data on file, previously unpublished]. This study included healthy volunteers (n = 260) and assessed the levels of CK during 12 weeks of treatment with monthly oral ibandronate (150 mg), weekly risedronate (35 mg; control group) and monthly placebo. The results of CK monitoring were consistent between active drugs and placebo throughout the study and no significant change in total serum CK level was elicited. These results show that monthly oral ibandronate 150 mg is unlikely to trigger an unexpected increase in total serum CK level in postmenopausal women.⁹

Efficacy

The goal of osteoporosis treatment is the prevention of all fracture types, including both vertebral and nonvertebral fractures. While vertebral fracture is the



most common osteoporotic fracture type, nonvertebral fractures such as those of the hip can be the most debilitating and costly. Thus the global assessment of efficacy of an anti-osteoporosis treatment requires an extensive evaluation of its anti-fracture efficacy at all skeletal-sites. Similarly, no prospective head-to-head trials, comparing the anti-fracture efficacy of the currently marketed bisphosphonates have been conducted, due to the large sample size such studies would require to reliably detect differences in fracture risk, and the associated high cost.⁵² Therefore, a valid assessment of the efficacy of a new bisphosphonate can be based on observational database analysis, which can provide sufficient sample size and permit the comparison of marketed doses in current clinical practice, allowing the evaluation of agents in a population with a broader range of characteristics than is typically permitted in a randomized clinical trial. Well-designed observational database studies have an important place in evidence-based medicine and can be used to compare the effects of bisphosphonates on clinical outcomes such as the risk of fracture.

Two meta-analyses to assess the anti-fracture efficacy of different doses of ibandronate have recently been completed utilizing slightly different methodologies. The first meta-analysis, conducted by a Canadian-based group and supported by a wider team of osteoporosis experts (Steering Committee for IbandronatE and Non-vertebral fraCture Endpoints: SCIENCE), used individual patient data from MOBILE^{32,33} and DIVA,^{40,41} trials of similar design, to assess the effect of different doses of ibandronate on non-vertebral fractures.⁵³ The varying doses used in the two studies were grouped based on annual cumulative exposure ($\text{ACE} = \text{dose} \times \text{dose frequency/year} \times \text{absorption factor}$ e.g. $150 \text{ mg} \times 12 \times 0.006 = 10.8 \text{ mg}$). This analysis showed a relative risk reduction in non-vertebral fracture rate of 38% when comparing combined doses (including monthly oral ibandronate 150 mg, quarterly i.v. ibandronate 3 mg and i.v. ibandronate 2 mg every 2 months [not licensed]) equivalent to an ACE of $\geq 10.8 \text{ mg}$ with an ACE of 5.5 mg (2.5 mg daily ibandronate). A dose-response effect was noted with increasing ACE (7.2–12 mg) compared with ACE 5.5 mg.

The second meta-analysis utilized individual patient data from four pivotal phase III clinical trials (i.v. dose fracture study,²⁹ BONE,²⁹ MOBILE,^{32,33}

and DIVA),^{30,32} all of which have been discussed individually above.⁵⁴ BONE and the i.v. dose fracture study were 3-year placebo-controlled fracture trials; MOBILE and DIVA were 2-year BMD active-comparator studies, which collected fracture data as safety measurements. Similar to the Canadian analysis, annual doses were grouped by ACE, i.e. high ($\geq 10.8 \text{ mg}$ includes 150 mg oral monthly, 3 mg i.v. quarterly, and 2 mg i.v. every 2 months), mid (5.5–7.2 mg) and low ($\leq 4.0 \text{ mg}$). However, rather than comparing to the low ibandronate dose group, this analysis compared reductions in fracture risk to placebo, using a combined placebo group from BONE and the i.v. dose fracture study. It was observed that the risk of clinical (vertebral and non-vertebral) and non-vertebral fractures was significantly reduced for doses of ibandronate with an ACE of $\geq 10.8 \text{ mg}$ compared with placebo. A significant reduction in risk associated with ibandronate was also demonstrated for a subgroup of six major non-vertebral fractures (clavicle, humerus, wrist, pelvis, hip and leg).

Based on the review of the efficacy profile of ibandronate summarized here, the evidence clearly supports the use of monthly oral ibandronate (150 mg) and quarterly i.v. injection ibandronate (3 mg) for the treatment of postmenopausal osteoporosis.

A meta-analysis pooled data from the four phase III clinical trials of ibandronate to assess the relationship between ibandronate dose, changes in bone mineral density, and rates of both clinical and non-vertebral fractures. Individual patient data from the intent-to-treat population of the BONE, IV fracture prevention, MOBILE, and DIVA studies were included for analysis. The relationship between ibandronate dose and bone mineral density at both the lumbar spine and at the total hip was assessed qualitatively. The relationship between lumbar spine bone mineral density and clinical fracture rate, and the relationship between total hip bone mineral density and non-vertebral fracture rate, were assessed both qualitatively and using mathematical models. A total of 8710 patients were included in this analysis. Both lumbar spine and total hip bone mineral density were observed to increase with increasing ibandronate dose. The incidence of all clinical fractures was observed to decrease as lumbar spine bone mineral density increased. A statistically significant inverse linear relationship was observed between percent



change in lumbar spine bone mineral density and the rate of clinical fractures ($P = 0.005$). A non-significant curvilinear relationship was observed between percent change in total hip bone mineral density and non-vertebral fracture rate. The authors concluded that increased ibandronate exposure is associated with increasing gains in the lumbar spine bone mineral density and decreasing clinical fracture rates and that a non-linear relationship may exist between increases in the total hip bone mineral density and non-vertebral fracture rate.⁵⁵

Although the efficacy of ibandronate had been demonstrated in clinical trials, alongside patient preference and adherence, 'real life' efficacy was still to be confirmed.

The eValuation of IBandronate Efficacy (VIBE) head-to-head database fracture study compared fracture rates between patients treated with monthly ibandronate and weekly oral bisphosphonates (BPs). This large study included women ≥ 45 years old, newly prescribed monthly oral ibandronate or weekly oral alendronate or risedronate, and without malignancy or Paget's disease of bone. The primary analysis included patients who were adherent to treatment during the first 90 days after the index date. The risks of hip, nonvertebral, vertebral and any clinical fracture were compared using Cox proportional hazards models and adjusted for potential confounding factors. A secondary, "intent-to-treat" analysis included all patients who received at least one BP prescription. Sensitivity analyses based on the primary analysis compared patients receiving ibandronate with patients receiving weekly alendronate or risedronate separately, and explored the effect of excluding patients with potential confounding factors from the analysis. Further sensitivity analyses varied the requirement for adherence during the first 90 days after the index date. The primary analysis population included 7345 monthly ibandronate and 56,837 weekly BP patients. Fracture rates after the 12-month observational period were $<2\%$ and fracture risk was not significantly different between patients receiving monthly ibandronate or weekly BPs for hip, nonvertebral or any clinical fracture (adjusted relative risk: hip = 1.06, $p = 0.84$; nonvertebral = 0.88, $p = 0.255$; any clinical fracture = 0.82, $p = 0.052$). Ibandronate patients had a significantly lower risk of vertebral fracture than weekly BP patients

(adjusted relative risk 0.36, 95% confidence interval 0.18–0.75, $p = 0.006$). In the secondary, "intent-to-treat" analysis, relative risks of fracture were not significantly different between treatment groups for any fracture type. The results of the sensitivity analyses were generally consistent with the primary analysis. This retrospective cohort study found that patients treated with oral monthly ibandronate or weekly BPs (alendronate and risedronate) had similar, low risks of hip fracture, nonvertebral fracture and any clinical fracture. Ibandronate patients had a significantly lower relative risk of vertebral fracture than weekly BP patients; the clinical implications of these findings require further exploration and validation.⁵⁶

Patient Preference

Randomised, controlled clinical trials are most frequently used to determine the efficacy and safety of a new drug or regimen. However, they do not describe how a regimen is perceived by patients, and therefore, the acceptability and use of a drug in clinical practice. Patient adherence to therapy for the treatment of chronic disease is poor; this is also true for oral bisphosphonates used to treat postmenopausal osteoporosis.⁵⁷ A study of 211,319 women receiving a prescription for a daily or weekly bisphosphonate (alendronate or risedronate) found that, following a steady decline throughout the 12-month study period, only 39% of patients receiving a daily regimen and 57% of patients receiving a weekly regimen were continuing treatment at the end of the study.⁵⁸ The consequences of poor adherence can be severe. A database study of 35,537 women receiving a bisphosphonate prescription reported that compliant patients, that is, those patients who had medication available for $\geq 80\%$ of the study, had a 21% lower fracture rate than those patients considered to be non-compliant ($p < 0.001$).⁵⁹ The adjusted risk was also significantly lower in compliant versus non-compliant patients when non-vertebral and hip fractures were considered separately (20% and 37%, respectively; $p < 0.001$ for both). An exhaustive search of the Belgian national social security database conducted in postmenopausal women, naïve to bisphosphonates, who received the first prescription of alendronate assessed the impact of persistence on hip fracture risk, using the Cox proportional hazards model. At 12 months, the rate of persistence was 39.45%.



For each decrease of the Medication Possession Ratio by 1%, the risk of hip fracture increased by 0.4% (OR: 0.996; CI 95%: 0.994–0.998; $p < 0.001$). The relative risk reduction for hip fracture was 60% (HR: 0.404; CI 95%: 0.357–0.457; $p < 0.0001$) for persistent compared to non-persistent patients.⁶⁰

The impact of a reducing bisphosphonate dosing frequency on therapeutic adherence has been documented in several studies. Data have shown that, although weekly dosing improves adherence compared to daily administration, levels are still suboptimal.⁶¹

Studies to assess adherence with the monthly oral ibandronate regimen have also been conducted. An open-label study and a database study including two databases (i3 Innovus and HealthCore) have compared monthly ibandronate with weekly bisphosphonates, alendronate and risedronate, and both studies reported improved rates of persistence with the monthly regimen.^{62,63} In the UK, open-label study ($n = 1,103$), a 47% relative improvement in persistence was reported for the monthly ibandronate group versus weekly alendronate ($p < 0.0001$).⁶² As per standard clinical practice in the UK, patients in the ibandronate group were enrolled into a patient support programme. The database study included a total of 3,512 and 13,967 women prescribed monthly ibandronate or weekly bisphosphonates, respectively, from the i3 Innovus claims database and 1,006 and 10,658 patients, respectively, from the HealthCore database.⁶³ After adjusting for age, co-pay and co-morbidities, monthly users were 25% and 38% less likely to discontinue therapy versus weekly users in the i3 Innovus and HealthCore analyses, respectively. Other persistence database studies comparing monthly and weekly bisphosphonate regimens have been completed.^{64,65} However, it is likely that differences in methodology, such as a lack of adjustment for confounding variables and not tailoring the refill gap for individual regimen dosing windows, have led to varying results from those summarized above.⁶¹

To further characterize the reported improved adherence with monthly versus weekly bisphosphonate regimens an open-label study (PRIOR) enrolled patients ($n = 543$) who had discontinued daily or weekly alendronate or risedronate due to perceived or actual GI intolerance.⁶⁶ On entering the study, patients were given the choice of receiving either monthly oral or quarterly i.v. ibandronate. Interestingly, 27% of

patients chose oral ibandronate and 73% of patients chose the i.v. regimen. Adherence rates were similar between both regimens (70% in the oral group and 83% in the i.v. group). Study patients reported a significant improvement in GI symptoms compared with baseline while receiving either form of ibandronate ($p < 0.0001$ for both). Another adherence study, BOHEMIA, assessed the impact of providing biofeedback, using bone turnover markers, on adherence in patients receiving monthly ibandronate ($n = 781$).⁶⁷ High adherence was reported in both study groups, those receiving biofeedback and those who were not (95% CI: 98.8%–99.8% and 95.5%–97.5%, respectively). When the two groups were compared, a statistically significant difference in favour of biofeedback was noted ($p < 0.001$).

In addition to treatment efficacy and possible side effects, patient preference is also likely to impact on long-term therapeutic adherence. In two 6-month, randomised, crossover, open-label studies (iBandronate ALendronate Trial in Osteoporosis: BALTO I and II) including a total of 692 patients, >70% of patients expressed a preference for the monthly oral ibandronate regimen versus the weekly alendronate regimen ($p < 0.0001$) and ~75% stated that the monthly ibandronate regimen was more convenient than the weekly alendronate regimen ($p < 0.0001$).^{68,69} The most common reasons for preferring the monthly regimen were greater ease of following the treatment regimen for a long-time and better lifestyle fit.

Place in Therapy

Since the mid-eighties, the management of osteoporosis has dramatically changed, from treatments that were either lacking anti-fracture efficacy (e.g. fluoride salts and etidronate) or linked to significant morbidity (e.g. estrogens), to new molecules combining reduction in fractures rates at various skeletal sites and positive risk-benefit ratios. Practitioners now have the opportunity to offer their patients a wide variety of appropriate treatments. However, most of the treatments developed between 1990 and 2000 were linked with poor adherence. Since adherence to therapy is a major determinant of the final outcome of drug management, the levels of benefit observed in real-life settings were quite different from those reported in randomised controlled trials. Subsequently, new chemical entities

were developed with the final objective of meeting patient's needs.⁷⁰

In the field of osteoporosis management and bisphosphonates, the most widely prescribed osteoporosis drugs worldwide, large surveys have identified adverse events and discomfort linked to regular intake of medication as the major drawbacks leading to poor adherence. Ibandronate was the first bisphosphonate for which anti-fracture efficacy had been unequivocally shown with dosing intervals greater than weekly. The monthly oral and quarterly IV injection formulations display anti-fracture efficacy similar to that obtained with daily or weekly oral bisphosphonates (i.e. alendronate and risedronate). Whereas the pivotal ibandronate study (BONE) concentrated on patients at high-risk of vertebral fractures, further analyses, including meta-analyses and real-life setting databases, have confirmed that the currently marketed doses (i.e. 150 mg monthly oral and 3 mg quarterly IV injection) have a positive effect on non-vertebral fractures, to the same extent as previously seen at the spine.

Adherence to treatment has been significantly improved (up to 51%) with monthly compared with weekly or daily administration of oral bisphosphonates,^{46,47} hence providing a solution to one of the major challenges in bisphosphonate management of osteoporosis.

Conclusions

Intermittent ibandronate with dose-free intervals of more than one week can be administered either orally or as an i.v. injection and therefore provides a new solution to the management of postmenopausal osteoporosis. Intermittent oral therapy is convenient and offers patients independence from close supervision, which benefits them, their physicians and the health services. Some patients, however, may need or prefer i.v. therapy perhaps because they are bed-bound or otherwise unable to follow strict dosing instructions. In such cases, an injection may be preferable to a prolonged infusion as it is likely to be less prone to complications. Thus availability of intermittent regimens of both oral and i.v. ibandronate is expected to provide physicians with the option of being able to tailor therapy to the needs of individual patients. These simple intermittent ibandronate dosing schedules are expected to optimally combine efficacy, tolerability and patient convenience. Their availability

should help optimize osteoporosis management in the 21st century.

Disclosures

The authors report no conflicts of interest.

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