Ibandronate: a new perspective in the treatment of osteoporosis

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Osteoporosis is a common, increasingly prevalent condition worldwide. Osteoporotic fractures are associated with substantial morbidity, mortality, and health service resource use. Current daily oral and weekly bisphosphonates are highly effective in managing osteoporosis but patients often fail to take their medication correctly and/or stop treatment prematurely. This poor adherence limits the benefits of bisphosphonates in routine clinical practice and adds to health service costs. More convenient bisphosphonate regimens, with a lower dosing frequency, would be predicted to improve adherence and optimize therapeutic benefits. Once-monthly oral and intermittent intravenous injection regimens now in late-stage clinical development for ibandronate show considerable potential to deliver these benefits.

Keywords: adherence, bisphosphonates, ibandronate, intermittent, intravenous, monthly, oral, osteoporosis

Role of bisphosphonates in osteoporosis

Osteoporosis is a chronic, progressive, systemic and mostly asymptomatic skeletal disease characterized by low bone mass and deterioration of bone micro-architecture, leading to an increased susceptibility to fragility fractures. The lifetime risk of such fractures in many Western countries is 30–40% [1] and they are associated with considerable morbidity [2] and mortality [3,4]. For example, the relative risk of mortality is estimated to be 60% higher in women with a prevalent vertebral fracture, versus those without [3]. Osteoporosis affects an estimated 75 million people in the US, Europe and Japan [5] and this already high prevalence is set to increase with the growth of the aging global population.

Consequently, osteoporosis has, and will continue to have, a major impact on health resources. Osteoporosis in women has been shown to result in more days in hospital per year than several other serious disorders, including myocardial infarction, breast cancer and chronic obstructive pulmonary disease (458,615 days compared with 131,331 days, 200,669 days and 353,654 days, respectively) [6]. Hospitalization and other treatment for osteoporotic fractures were estimated to cost US$17 billion in the US in 2002 [7]. In the European Union, hospital costs for hip fractures alone were Euro 3.6 billion in 1996 increasing to Euro 4.8 billion in 1999 [8].

Bisphosphonates are widely used as first-line therapy in osteoporosis management, due to their excellent anti-fracture efficacy and generally good tolerability. In trials conducted in postmenopausal women, bisphosphonates have been shown to significantly suppress biochemical markers of bone resorption [9–14] and thereby to increase bone mineral density (BMD) at the lumbar spine, hip and forearm [9–11]. The bone resorption suppression and BMD increases result in clinically significant reductions in the risk of new vertebral fractures of 41–62% [9–11,15]. Significant risk reductions in non-vertebral (20–69%) [10,15–17] and hip (30–51%) fractures [9,16] have also been reported.

Poor adherence to therapies used in the management of chronic diseases is an immense problem

Adherence, a term used to encompass both compliance and persistence with medication, is often poor, particularly in chronic diseases such as osteoporosis. Compliance, that is how often patients take their medication correctly, is optimal in only about half of all patients on long-term treatment, regardless of the disorder [18,19]. Persistence, that is how long patients persevere with medication, diminishes over time [20,21].

Non-response to medication is often attributable to suboptimal adherence and can lead to exacerbations or complications of the underlying illness. For example, increased mortality, transplant rejection, breakthrough seizures and schizophrenia relapse are associated with poor adherence to cardiovascular drugs [22], immunosuppressives [23], anti-epileptics [24] and anti-psychotics [25], respectively.

As a result of this treatment failure, poor therapeutic adherence adversely impacts healthcare systems, leading to increased costs due to therapy changes, extra consultations and laboratory tests [26]. Breakthrough symptoms are estimated to

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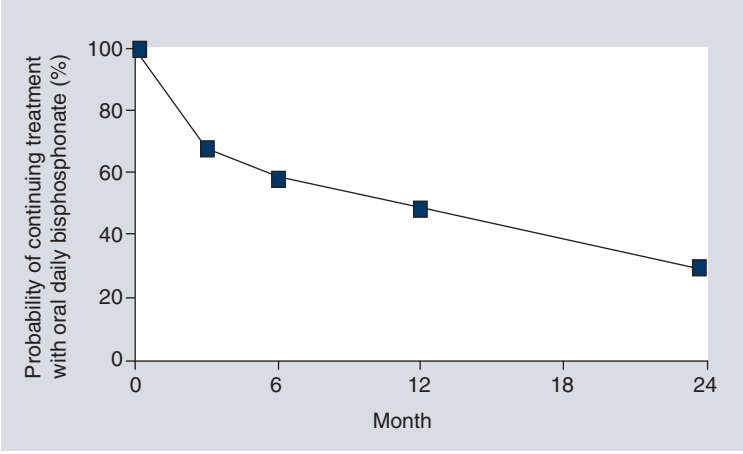
account for at least 10% of all hospitalizations and almost a quarter of all nursing home admissions [27]. In total, non-adherence was estimated to be responsible for US$18 billion in the US in 1986 in direct hospital costs and a further US$17–25 billion in indirect costs [26].

Adherence to current bisphosphonates is suboptimal

Adherence to current bisphosphonates is a major problem in osteoporosis management. Current oral bisphosphonates must be taken according to strict instructions designed to optimize tolerability and bioavailability, and which require patients to remain fasting and upright, and to drink no fluid other than water for 30 minutes after taking their tablets. The need to follow these directions every time medication is taken, that is daily or weekly, will be unacceptably disruptive or at least inconvenient for many patients. The potential of current oral bisphosphonates to cause upper gastrointestinal (GI) adverse events may also impair therapeutic adherence [28–30].

As a consequence, persistence with current daily oral bisphosphonates for osteoporosis management is low and deteriorates over time. In a study of 401 postmenopausal women with osteoporosis or osteopenia, 13% of those prescribed daily oral alendronate did not even start treatment [28]. For the women who did start therapy, the probability of continuing was 49% and 30% after 1 year and 2 years, respectively (Figure 1). In another study of more than 1,800 patients with osteoporosis, a fifth stopped treatment in the first four months [31].

Figure 1. The probability of continuing bisphosphonate treatment decreases significantly over time [28].



Although the introduction of weekly bisphosphonate regimens has improved persistence to a certain degree, overall it remains suboptimal. For example, in two recent studies, 13% and 17% of patients, respectively, discontinued weekly alendronate within 6 months of starting therapy [32,33]. In two other studies, only 50% of patients remained on weekly therapy with either alendronate or risedronate after 1 year [34,35].

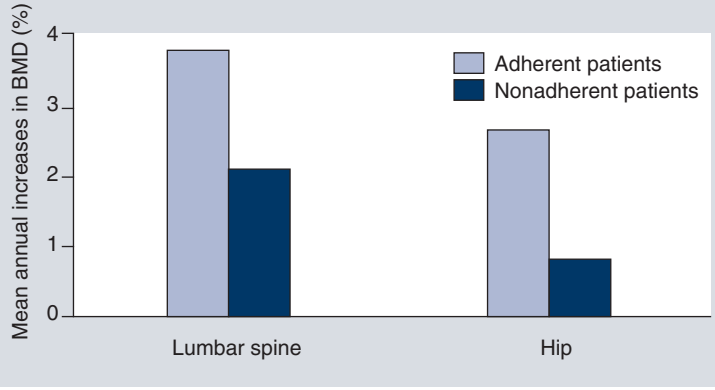
The clinical impact of poor adherence to the bisphosphonates

Poor adherence to bisphosphonate therapy results in suboptimal changes in bone turnover, BMD and, ultimately, fracture risk, as demonstrated by several recent studies. For example, an analysis from the Improving Measurements or Persistence of Actonel Treatment (IMPACT) database of 2,302 women with postmenopausal osteoporosis showed that the majority of patients (more than 60%) who adhered to bisphosphonate treatment could achieve a clinically significant decrease of more than 50% in bone resorption marker levels. Only 20% of the non-adherent patients achieved this level of suppression, however [36]. This finding indicates that the reduction in bone resorption rate is insufficient in poorly adherent patients.

Similarly, in a study of 176 women with osteoporosis, those who complied with at least two-thirds of their bisphosphonate medication achieved significantly greater BMD gains at the lumbar spine and hip than those who were less compliant [37]. Compliant patients achieved significantly greater gains in spinal and hip BMD (3.8% and 2.6%, respectively) compared with those patients with poor compliance (2.1% [$p<0.005$] and 0.8% [$p<0.0056$], respectively) (Figure 2). In another study (an audit of 240 patients), compliant women achieved BMD gains of 4.3% and 1.2% at the lumbar spine and hip compared with only 2.8% and 0.3%, respectively, in the less compliant individuals [38]. A third study, of 4,405 patients with osteoporosis, reported significant increases in lumbar spine BMD, from baseline, after 3 years of 6.5% in those patients who were compliant [39]. In contrast, after 3 years, inconsistent and non-compliant bisphosphonate users demonstrated modest gains of only 3.2% [39].

The most important evidence of the adverse clinical impact of poor adherence is that it ultimately hinders therapy from effectively reducing fracture risk. In an extensive, retrospective study of 11,249 women with osteoporosis, poor compliers were defined as those taking less than 80% of their prescribed medication. These women ran a significantly greater risk of fractures (16% greater risk;

Figure 2. Poor adherence to bisphosphonate medication affects BMD [37].



§: p < 0.0056 versus non-adherent; §§: p < 0.004 versus non-adherent.

95% confidence intervals: 5%, 25%) than the compliant patients [40]. Poor compliance also significantly increased hospitalization rates (52.4% vs. 42.6%, p<0.0001) leading to a 14% rise in medical services costs [40].

Similar findings were observed from an analysis of a US claims database, which was examined to assess the effect of adherence to a bisphosphonates regimen on fracture risk [41]. Data from 3,720 patients receiving bisphosphonate treatment demonstrated that adherent patients are at a significantly lower risk of fractures at the spine (odds ratio R=0.601; p≤0.05) and hip (odds ratio=0.382; p<0.05), vs. non-adherent patients.

Collectively, this evidence strongly indicates that poor adherence to treatment undermines the therapeutic efficacy of bisphosphonates. Conversely, improving adherence would be predicted to improve outcomes in clinical practice.

Ibandronate: development of less frequent regimens & alternative dosing options for osteoporosis management

Regimens with a lower dosing frequency would be expected to promote adherence to bisphosphonate therapy and, therefore, optimize patient management, as has been demonstrated in numerous other therapeutic areas [32,42,43]. Indeed, in osteoporosis, weekly bisphosphonate dosing regimens already have partly addressed the problem of adherence. Of women with postmenopausal osteoporosis participating in a 9-week crossover study, 88% felt it would encourage them to comply better in the long term [44]. However, reducing the dosing frequency from daily to weekly is only the first step to optimizing bisphosphonate therapy. This is because, although weekly regimens have improved adherence, weekly bisphosphonates are still associated with unacceptably high discontinuation rates: 50% of patients discontinue therapy within 12 months [34,35]. Given that an improvement has been seen with less frequent dosing regimens, it is likely that bisphosphonates offering dosing intervals of more than a week would disrupt patients' lives less, be more convenient and thus promote even greater adherence.

For oral bisphosphonates, less frequent dosing may also reduce the likelihood of upper GI adverse events by reducing exposure to the tablets and allowing longer for any irritation to heal. These potential benefits emerged from preclinical studies indicating that upper GI side effects from oral bisphosphonates are largely due to prolonged contact with the tablet and/or reflux [45,46]. Extended contact with tablets, even placebo, can irritate the esophageal mucosa. Acid reflux containing bisphosphonate increases the likelihood of such damage. Either of these factors may exacerbate or delay healing of previous esophageal injury, a known adverse event risk factor. Less frequent oral dosing would both reduce tablet exposure and increase the time between doses for esophageal mucosal regeneration. Since upper GI adverse events are a major reason for discontinuation of oral bisphosphonate treatment [28,29,47], a regimen with the potential to reduce the incidence of such events would be predicted to improve therapy adherence.

Ibandronate, a potent, nitrogen-containing bisphosphonate [48,49], has been developed to address the unmet needs in osteoporosis management by providing a convenient, more patient-friendly dosing regimen to optimize therapeutic adherence. Two simple intermittent ibandronate regimens are in late-stage clinical development: a once-monthly oral tablet and an intermittent intravenous (i.v.) injection [49–52].

Monthly oral ibandronate: investigating the concept of extended between-dose intervals

Oral ibandronate currently is the most comprehensively evaluated bisphosphonate for administration in beyond-weekly dosing regimens. Intermittent oral ibandronate was first investigated in a double-blind, placebo-controlled, phase II study, conducted in 240 women with postmenopausal osteoporosis [53]. Patients received either intermittent oral ibandronate (20 mg every other day for 12 doses, followed by 9

weeks of no drug) or daily oral ibandronate (2.5 mg). Calcium and vitamin D supplementation was provided to both treatment groups. After 2 years, lumbar spine BMD increases in both regimens were equivalent with 5.5% and 5.6% in the intermittent oral and daily oral ibandronate groups, respectively, compared with baseline. Both ibandronate arms also produced comparable increases in BMD at the total hip (3.4% in both arms). Additionally, biochemical markers of bone turnover decreased significantly and comparably in the two active treatment arms.

Following the positive findings from this study, 'proof of concept' for antifracture efficacy with an intermittent oral ibandronate regimen was prospectively evaluated in a 3-year, multinational, double-blind, phase III, fracture prevention study of oral ibandronate: the oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE). The BONE study, conducted in 2,946 women with postmenopausal osteoporosis, examined the efficacy and safety of oral ibandronate administered daily or with a between-dose interval greater than 2 months (20 mg every other day for 12 doses every 3 months) [15]. In this trial, the intermittent oral ibandronate regimen demonstrated comparable vertebral antifracture efficacy (primary efficacy endpoint) to the daily oral regimen. The rate of new vertebral fractures after 3 years was 4.9% in the intermittent arm, 4.7% in the daily arm and 9.6% in the placebo arm. Relative to placebo, the risk of new morphometric vertebral fractures was reduced by 50% (p=0.0006) and 62% (p=0.0001), respectively, in the intermittent and daily oral ibandronate arms (Figure 3). Additionally, oral ibandronate significantly reduced the relative risk of clinical vertebral fracture by 48% in the oral intermittent arm and 49% in the daily oral arm. This is the first and as yet only time that an osteoporosis medication has been prospectively proven to offer a lasting antifracture efficacy in a regimen with a dosing interval of greater than 2 months in the overall population of a randomized, controlled trial. The significant antifracture effect observed with oral ibandronate was observed regardless of patient demographics, baseline fracture risk [54], or fracture severity [55].

No significant non-vertebral antifracture effect was observed in the overall population of the BONE study after 3 years (secondary efficacy endpoint). As the BONE study was not designed to evaluate non-vertebral antifracture efficacy and the study population was at low risk for such fractures (based on baseline femoral neck BMD T-scores), this finding was not unexpected. In a patient subgroup at higher risk for such fractures (baseline femoral neck BMD T-score <3.0), daily oral and intermittent oral ibandronate reduced the risk of non-vertebral fractures by 69% (p=0.012) and 37% (p=0.22), respectively [15].

As well as reducing fracture risk, both ibandronate regimens provided similar and significant increases in BMD at the lumbar spine and hip, and substantial and sustained reductions in biochemical markers of turnover. After 3 years and relative to baseline, BMD at the lumbar spine increased by 5.7%, 6.5% and 1.3% in the intermittent, daily and placebo arms, respectively, (p<0.0001 for both ibandronate arms vs. placebo) [15]. At the same time, BMD at the total hip increased by 2.9% and 3.4% with intermittent and daily oral ibandronate, compared with a loss of 0.7% in the placebo group (p<0.0001 for both ibandronate arms vs. placebo) [15]. A pronounced reduction in biochemical markers of bone resorption (CTX/creatinine and NTX/creatinine) and formation (serum osteocalcin and bone-specific alkaline phosphatase) was evident in both ibandronate groups as early as 3 months after the start of treatment and was sustained throughout the

Figure 3. The BONE study of oral ibandronate: effect of daily oral and intermittent ibandronate on vertebral fracture incidence in postmenopausal osteoporosis after 3 years [15].

§: Relative risk reduction versus placebo (95% CI): 62% (41–75; p = 0.0001); §§: Relative risk reduction versus placebo (95% CI): 50% (26–66; p = 0.0006).

rest of the study ($p<0.0001$ for all bone markers vs. placebo after 3 years) [15].

Both regimens were well tolerated, with safety profiles similar to placebo [15], notably even in patients with a history of upper GI disorders or taking concomitant non-steroidal anti-inflammatory drugs (NSAIDs) [56]. The frequency of upper GI adverse events in the overall study population was 27%, 25% and 25% in the placebo, daily and intermittent ibandronate arms, respectively (Figure 4). Furthermore, in patients with a history of GI disorders and in those taking NSAIDs, the incidence of upper GI adverse events consistently remained comparable between the placebo, daily and intermittent groups.

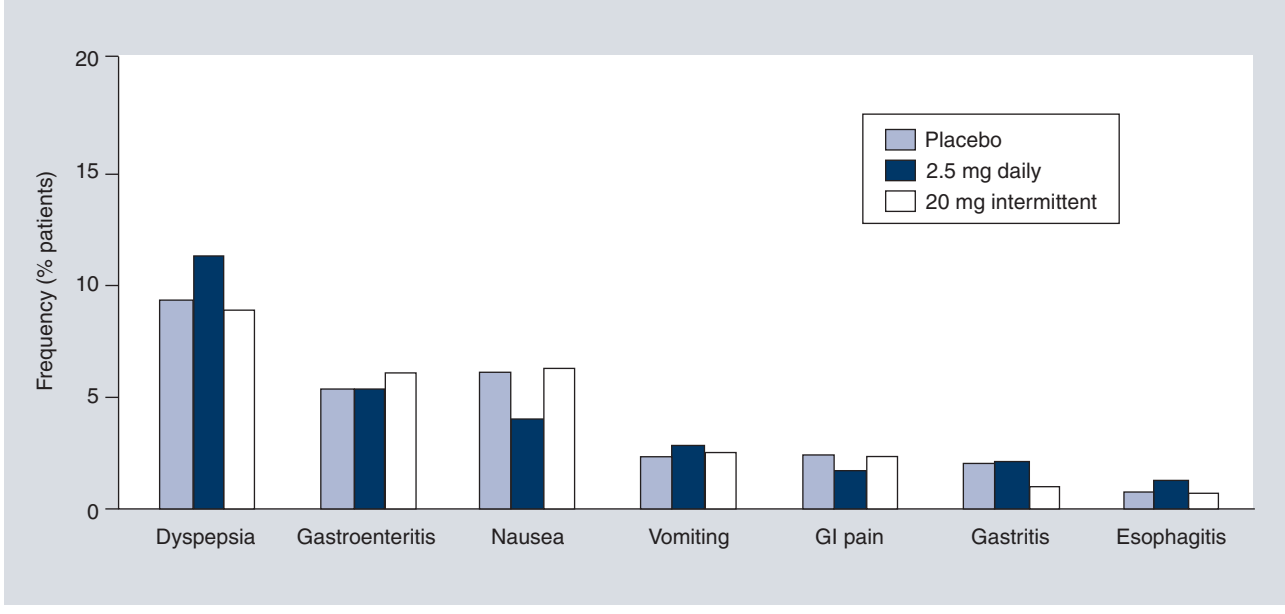
The findings from the BONE study thus establish the feasibility of providing significant antifracture efficacy with ibandronate when administered less frequently than daily or weekly. Accordingly, trials have been initiated to investigate two simple ibandronate regimens in postmenopausal osteoporosis: a once-monthly oral regimen of ibandronate and intermittent i.v. ibandronate injections.

Once-monthly oral ibandronate: a new paradigm in osteoporosis management

Although weekly bisphosphonate dosing appears to improve adherence compared with daily regimens, further reduction in dosing frequency to once monthly would probably further increase patient acceptability and adherence while providing the efficacy of daily or weekly administration. Once-monthly oral ibandronate is therefore predicted to combine optimal efficacy, tolerability and convenience.

In a double-blind, placebo-controlled, phase I, dose-ranging study, the Monthly Oral Pilot Study (MOPS) [57], 144 postmenopausal women were randomized to receive three cycles of either placebo, or oral ibandronate (50 mg, 100 mg or 150 mg) given once monthly (every 30 days); patients were not provided with daily calcium and vitamin D supplementation. Influenza-like illness symptoms have been observed in some patients receiving nitrogen-containing bisphosphonates for the first time. Therefore, after the first cycle and to separate the effects of dose and first-time treatment, the 50 mg ibandronate arm was split in a randomized, double-blind fashion into two arms, with participants continuing on either 50 mg or 100 mg ibandronate. The chosen dosing regimens were selected on the basis of clinical study experience [15,58,59] and clinical trial simulation [60]. The clinical trials data indicate that although daily oral and intermittent bisphosphonate regimens providing the same cumulative dose over a given time period offer comparable efficacy, a more extended dosing interval (i.e., beyond weekly) might require a somewhat higher cumulative dose to optimize this efficacy. MOPS therefore included doses

Figure 4. Change in (A) lumbar spine BMD and (B) urinary CTX (vs. placebo) at 1 year in IRIS, the i.v. fracture-prevention study and BONE [15,71,72].



higher than the cumulative monthly dose provided by the daily regimen, i.e., greater than 75 mg. Simulated biomarker responses for a range of monthly oral ibandronate regimens supported this conclusion, indicating that monthly oral ibandronate at doses of 100 mg and 150 mg produces sustained residual suppression (i.e., 1 month after dosing) in urinary CTX [60].

The results from MOPS indicate that monthly oral ibandronate is well tolerated with a safety profile similar to placebo. Importantly, there was no apparent relationship between adverse events and dose. The favorable tolerability profile of these relatively higher oral ibandronate doses is supported by the findings from a study that administered 50 mg oral ibandronate every day to patients with metastatic bone disease for 96 weeks [61]. In this study, tolerability was comparable to placebo.

In addition to being well tolerated, the monthly oral ibandronate regimens investigated in MOPS significantly reduced biochemical markers of bone resorption and exhibited a clear dose-response relationship for the area under the effect curve (AUEC) for median relative change [62]. This analysis is an integrated pharmacodynamic assessment reflecting the total level of suppression over the study period (days 1 to 91).

The MOPS findings highlight a potential role for monthly oral ibandronate in the management of postmenopausal bone loss. However, because of the small number of participants and the lack of standardized calcium and vitamin D supplementation in this study, a larger, randomized, double-blind trial is ongoing to further investigate this regimen: the Monthly Oral iBandronate In LadiEs (MOBILE) study [63]. MOBILE is a multinational, phase III, non-inferiority study to compare the efficacy and safety of once-monthly oral ibandronate with the daily ibandronate regimen (62% new vertebral fracture risk reduction) in postmenopausal women with osteoporosis. Women are receiving daily oral (2.5 mg) ibandronate or monthly oral ibandronate at a dose of either 100 mg (as a single dose or two doses or 50 mg on consecutive days) or 150 mg (as a single dose), with monthly or daily oral placebo tablets as appropriate. All participants are also receiving daily calcium (500 mg) and vitamin D (400 IU/day).

The MOBILE study is utilizing a non-inferiority analysis, based on changes in lumbar spine BMD, to compare the efficacy of the monthly oral regimens to daily oral ibandronate. Non-inferiority testing is well accepted for investigating therapeutic equivalence between regimens. Most notably, recent studies used non-inferiority or equivalent analyses to compare the efficacy of daily oral and weekly oral bisphosphonate regimens [58,59]. The positive outcomes from these studies, which like MOBILE also used mean percent change in lumbar spine BMD change as a primary study endpoint, led to the subsequent licensing and rapid uptake, of weekly oral bisphosphonates in clinical practice.

In MOBILE, equivalent efficacy will be inferred if the increases in lumbar spine BMD observed after 1 year with the monthly oral ibandronate regimens are shown to be non-inferior to those observed with the daily oral ibandronate regimen, which has proven antifracture efficacy. Based on previous studies, the minimum difference in lumbar spine BMD produced between placebo and the 2.5mg daily oral ibandronate dose at 1 year is estimated to be 3.3% [15,53,64]. In MOBILE, the tolerance boundary for non-inferiority was set as 30% of this difference, i.e., 1.0%. Thus, non-inferiority would be concluded if the lower boundary of the one-sided 97.5% confidence interval in mean percent change in lumbar spine BMD, between the monthly, and 2.5 mg daily, oral ibandronate regimens were ≥–1.0%.

Positive outcomes from MOBILE will demonstrate the clinical utility of once-monthly oral ibandronate in the treatment of postmenopausal osteoporosis, which will likely provide an effective, yet patient-friendly, alternative to conventional daily and weekly oral bisphosphonates.

Intermittent i.v. ibandronate injections

Oral bisphosphonate administration is likely to remain the most appropriate therapy option for the majority of patients as it can be self administered. However, i.v. administration may be the preferred option for patients who are confined to bed or who otherwise cannot comply with the stringent postural requirements of oral regimens. It may also be more suitable for those who cannot tolerate, or swallow, oral bisphosphonates. There are several other advantages to i.v. administration over oral formulations: they must be given by a health professional, which ensures compliance; they avoid the possibility of upper GI adverse events, and the need to follow strict dosing instructions.

Due to its high potency [48], tolerability and favorable binding characteristics [68], ibandronate can be given by rapid (over 15–30 seconds)

i.v. injection. To date, no cases of serious renal side effects, including acute renal failure, have been attributable to the use of i.v. ibandronate. This contrasts with other intravenously administered bisphosphonates that must be given by prolonged i.v. infusion to avoid adverse renal effects. Zoledronate, for example, another highly potent bisphosphonate, has been associated with renal complications even when given at its licensed dose in oncology (4 mg by i.v. infusion over 15 minutes) [66,67].

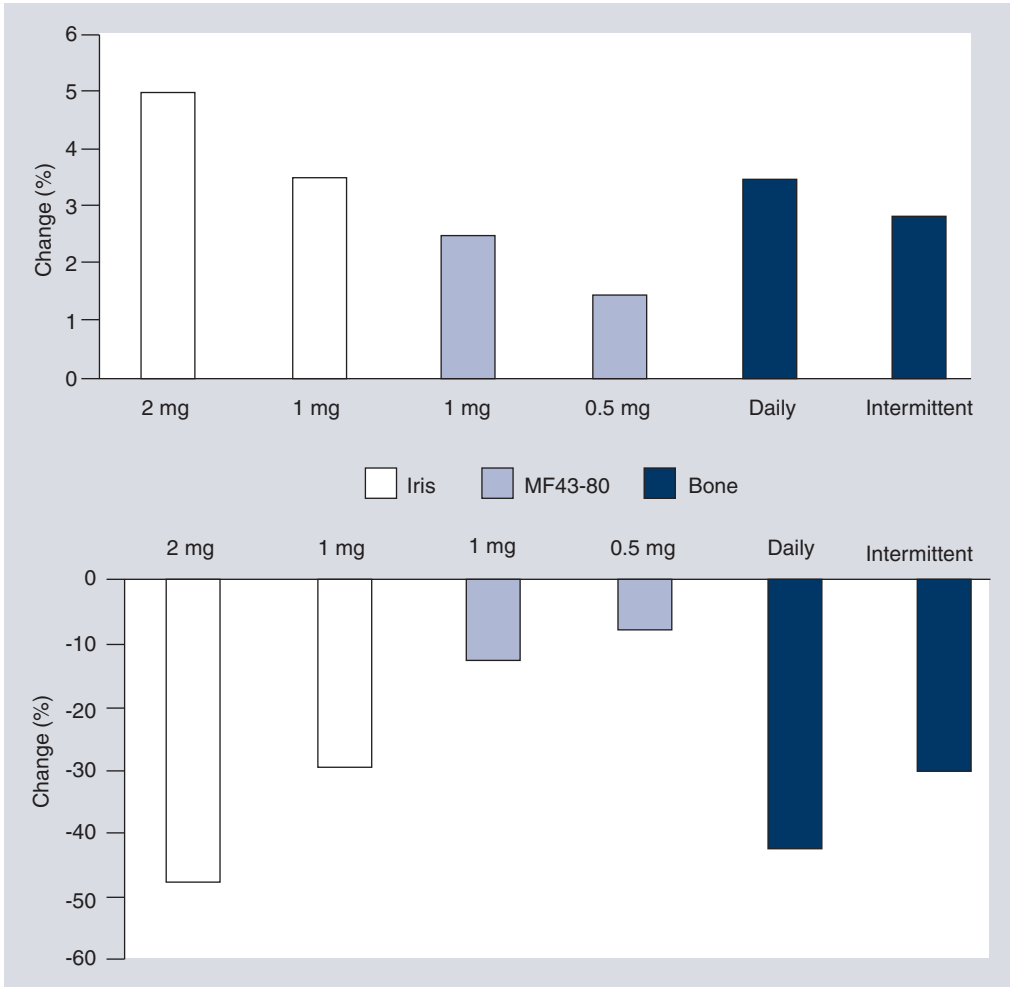
Preclinical [68] and early clinical studies [69,70] demonstrated the clinical potential of i.v. ibandronate to be given by injection rather than infusion, and in regimens with extended between-dose intervals. In a 1-year randomized, placebo-controlled, phase II dose-ranging study, in 126 women with postmenopausal osteoporosis [70], 0.25 mg, 0.5 mg, 1 mg or 2 mg ibandronate i.v. injections given once every 3 months dose-dependently increased lumbar spine BMD by 2.4%, 3.5%, 3.7% and 5.2%, respectively, relative to baseline, and compared with an increase of 0.9% in the placebo group. The BMD gains with ibandronate were accompanied by substantial reductions in urinary CTX and serum osteocalcin. I.v. ibandronate was well tolerated, with no significant safety concerns identified.

A subsequent 3-year, placebo-controlled study investigated the antifracture effect of ibandronate 0.5 mg and 1 mg given once every 3 months [71]. After 3 years, significant dose-dependent increases in lumbar spine BMD of 3.9% and 4.9%, respectively, were observed in the two ibandronate arms compared with an increase of just 1% in the placebo arm. Similarly, significant dose-dependent BMD gains of 1.1% and 2.3% were seen at the total hip in the two ibandronate groups, respectively, compared with a loss of over 1% in the placebo group. At the same time, there was a dose-dependent suppression of biochemical markers of bone resorption and formation. However, the magnitude of the treatment effect on BMD and bone turnover markers was lower than that observed in the BONE study in which highly significant reductions in vertebral fracture incidence were observed with ibandronate therapy [15]. Consequently, the reduction in the incidence of new vertebral fractures from 10.7% in the placebo arm to 8.7% and 9.2% in the 0.5 mg and 1 mg ibandronate arms, respectively, did not reach statistical significance. As dose-dependent BMD gains and biomarker reductions were consistently observed, it is likely that the 0.5 mg and 1 mg 3-monthly doses were suboptimal and that higher doses are needed for antifracture efficacy.

Therefore, to facilitate further investigation into the dose-response relationship of 3-monthly i.v. ibandronate injections, the Intermittent Regimen Intravenous Ibandronate Study (IRIS) was initiated. In the IRIS study, 520 women with postmenopausal osteoporosis were randomized to receive i.v. injections of either 2mg or 1mg ibandronate or placebo once every 3 months [72]. After 1 year, ibandronate therapy produced substantial and dose-dependent increases in lumbar spine and hip BMD, and decreases in biochemical markers of bone turnover. The 2 mg dose was significantly more effective than the 1 mg dose (used in the earlier, fracture-prevention study of i.v. ibandronate) [71] (Figure 5). Lumbar spine BMD increased by 5.0% and 2.8% in the 2 mg and 1 mg groups, respectively, and decreased by 0.04% in the placebo group. Total hip BMD increased by 2.9%, 2.2% and 0.6%, respectively. Serum and urinary CTX decreased by 63% and 61% respectively with the 2 mg dose and by 44% and 42%, respectively, with the 1 mg dose. Notably, the 2 mg dose provided similar bone resorption suppression and lumbar spine BMD gains to those seen after 1 year in the BONE study (Figure 5), in which daily oral ibandronate achieved a fracture risk reduction of 62%. Furthermore, the changes in BMD and bone resorption observed with 2 mg i.v. ibandronate were consistent with those seen with other oral bisphosphonates with antifracture efficacy [11–14,73].

In both of the above studies, i.v. ibandronate was well tolerated, with a similar overall safety profile to placebo. In the i.v. antifracture study, only myalgia (7.1% and 5.1% in the 1 mg and 0.5 mg arms, respectively, versus 3.4% in the placebo arm) and injection site reactions (2.5% and 2.3%, respectively, versus 0.1%) were more commonly reported as treatment related in the active treatment arms versus placebo. Likewise, in the IRIS study, only pain/pain in extremity (2–3%, versus 0.1%), arthralgia (3% versus 1%) and myalgia (2% versus 0%) were reported with a higher frequency in the active treatment arms. In both studies, such events generally occurred with the initial administration only, were transient in nature and resolved without symptomatic treatment. Importantly, no indicators of renal toxicity (creatinine or urea in serum) were detected with i.v. ibandronate therapy.

Figure 5. Change in (A) lumbar spine BMD and (B) urinary CTX (both vs. placebo) at 1 year.



Given the strong dose-response relationships for BMD and bone markers shown in the phase II dose-finding study, the IRIS study, and the fracture-prevention trial of i.v. ibandronate, antifracture efficacy may be likely with doses equal to or greater than 2 mg, given once every 3 months. The findings in a study in patients with corticosteroid-induced osteoporosis receiving 2 mg i.v. ibandronate injections every 3 months [74] further support this prediction. In this study, a 62% reduction in the risk of new vertebral fractures was observed in the patients receiving 3-monthly i.v. ibandronate injections compared with daily oral alfacalcidol.

To further investigate the efficacy and safety of intermittent i.v. ibandronate injections in the treatment of postmenopausal osteoporosis, and to optimize the dose and dosing interval, alternative intermittent i.v. injection regimens are being investigated in the multicenter non-inferiority Dosing Intra-Venous Administration (DIVA) trial [75]. DIVA is a randomized, double-blind, double-dummy, parallel-group, non-inferiority study in a total of 1,395 women to compare the efficacy and safety of two ibandronate i.v. injection regimens (2 mg once every 2 months and 3 mg once every 3 months) with the proven daily oral ibandronate regimen. All participants are also receiving daily calcium and vitamin D supplements. The primary efficacy endpoint is the relative change from baseline in lumbar spine BMD after 1 year. Secondary efficacy endpoints include BMD at additional sites and a biochemical marker of bone turno-

Executive summary

- Bisphosphonates are efficacious for the treatment of osteoporosis. However, poor adherence to current oral bisphosphonates compromises therapeutic outcomes.
- Reducing the dosing frequency can improve adherence.
- Ibandronate is a potent, nitrogen-containing bisphosphonate that can be administered with between-dose intervals longer than weekly.
- In the iBandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE) study, an intermittent regimen of oral ibandronate with a between-dose interval of greater than 2 months provided comparable antifracture efficacy to a conventional daily regimen in women with postmenopausal osteoporosis (50 and 62% vertebral fracture risk reduction, respectively, at 3 years).
- Recently, the feasibility and clinical potential of a once-monthly oral ibandronate regimen was demonstrated in the Monthly Oral Pilot Study (MOPS).
- The noninferiority study, Monthly Oral iBandronate In LadiEs (MOBILE), will compare the clinical efficacy and safety of once-monthly oral ibandronate to an established daily regimen in women with postmenopausal osteoporosis.
- For patients not suited to oral administration, ibandronate has demonstrated efficacy and safety as an intermittent intravenous injection.
- The Dosing IntraVenous Administration (DIVA) trial will further optimize this intermittent intravenous ibandronate dosing regimen and investigate its efficacy and safety compared with the daily oral regimen.

ver (serum CTX). Additionally, bone biopsies and histomorphometric analysis will assess the effects of ibandronate on bone quality.

The non-inferiority test that is being applied in the DIVA study is identical to that used in the MOBILE study (based on a comparison of 1-year BMD changes at the lumbar spine). Thus, for the same reasons explained earlier in this review for the MOBILE study, the findings from DIVA will establish the efficacy of i.v. ibandronate injections in women with postmenopausal osteoporosis.

Expert opinion

Current daily oral and weekly bisphosphonates are highly effective in the management of osteoporosis, but poor long-term adherence limits their benefits in day-to-day clinical practice. Given the evidence, less frequent dosing, which is more convenient and less disruptive, will likely further improve patient convenience and acceptability. Thus, the monthly oral and intermittent i.v. injection regimens of ibandronate that are under clinical investigation are expected to be more acceptable to patients than current treatment. Ultimately, this will likely support improved treatment adherence, leading to optimal therapeutic benefits for the patient.

Outlook

Vertebral and hip fractures are the major complications of osteoporosis and are associated with pronounced morbidity and increased mortality. Although several agents have been used for many years in the prevention or treatment of osteoporosis, an appropriate demonstration of antifracture efficacy has only become available within the last 15 years. Several compounds have now demonstrated an ability to reduce vertebral (oral bisphosphonates, selective estrogen receptor modulators, teriparatide, calcitonin, strontium ranelate and D-hormones), nonvertebral (oral bisphosphonates, teriparatide, strontium ranelate, calcium and vitamin D and D-hormones), or hip (oral bisphosphonates, strontium ranelate and calcium and vitamin D) fractures. Currently, the decision-making process involved in selecting a particular therapeutic option is dependent on the stage of the disease and the respective risk of vertebral and nonvertebral fractures. However, one of the major challenges faced by practitioners is the poor compliance of patients to anti-osteoporotic therapies. The development of new chemical entities, or new routes of administration that are well tolerated, is of paramount importance. Similarly, medications that can be taken without major constraints and that are considered to be userfriendly by the patients will improve compliance and, subsequently, the final therapeutic outcomes of the treatment.

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