EXPERT OPINION

Osteoporosis treatment: why ibandronic acid?

Maurizio Rossini†, Giovanni Orsolini, Silvano Adami, Vidya Kunnathully & Davide Gatti

University of Verona, Department of Medicine, Rheumatology Section, Policlinico Borgo Roma, Verona, Italy

Introduction: In this article, we have summarized the specific evidence on ibandronic acid (or ibandronate) efficacy, tolerability, and feasibility acquired from trials and clinical use.

Areas covered: This critical review focuses on evidence from randomized controlled clinical trials, meta-analyses, surrogate markers, bridging trials, long-term extension studies, observational studies, clinical experiences in osteoporosis in addition to postmenopausal treatment adherence in clinical practice, and safety profile of ibandronic acid.

Expert opinion: Pivotal studies on ibandronic acid efficacy in terms of antifracture effects on nonvertebral fractures had some intrinsic limitations. However, a large body of indirect evidence suggests that ibandronate has significantly sustained vertebral and nonvertebral antifracture efficacies in women with postmenopausal osteoporosis, in comparison to those observed with other nitrogen-containing bisphosphonates. Discrepancies in efficacy between the available bisphosphonate regimens appear to be a function of dose rather than to inherent differences in their respective therapeutic potential. Drugs or treatment regimens that minimize the risk of osteoporotic fractures and make the treatment of osteoporosis more convenient and suitable for patients are preferred: ibandronic acid marketed at oral doses of 150 mg once monthly and 3 mg quarterly as intravenous injection has these characteristics. The safety profile of ibandronic acid treatment appears to be good overall and in some cases better than that of other nitrogen-containing bisphosphonates.

Keywords: bone turnover markers, fracture, ibandronate, ibandronic acid, osteoporosis

Expert Opin. Pharmacother. (2013) 14(10):1371-1381

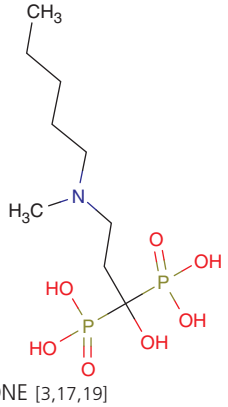
1. Introduction

Fractures are the key clinical feature of osteoporosis and their prevention in the treatment of the disease is of vital importance because of the negative clinical, social, and economic implications osteoporotic fractures have on patients and healthcare systems. The nitrogen-containing bisphosphonates (N-BPs) have proven antifracture efficacy for the treatment of osteoporosis [1-4], and they are the preferred treatment option for this disease [5]. In this article, we summarized the evidence on ibandronate efficacy, tolerability, and feasibility acquired from trials and clinical use. Four different levels of supportive evidence from trials are utilized in this review: information from randomized clinical trials, from meta-analyses of clinical trials, clinical trials using surrogate markers, and observational studies. The most reliable way of gathering evidence of antifracture efficacy is directly from randomized clinical trials, which contain large patient cohorts and are designed specifically to control the chance of potential biases. However, it is becoming ethically unacceptable to perform randomized controlled trials versus placebo in populations at high risk for fracture [6,7]. Thus, it has been harder for the most recently investigated

informa
healthcare

10.1517/14656566.2013.795949 © 2013 Informa UK, Ltd. ISSN 1465-6566, e-ISSN 1744-7666

Box 1. Drug summary.

Drug name	Ibandronic acid
Phase	Launched
Indication	Treatment and prevention of postmenopausal osteoporosis
Pharmacology description	Nitrogen-containing bisphosphonate
Route of administration	Oral or parenteral (intravenous injection); intermittent regimen
Chimical structure	
Pivotal trials	BONE [3,17,19] IV Fracture Study [15] MOBILE [55,56,58] DIVA [52,54,60]

drugs, such as ibandronate, to demonstrate an antifracture efficacy, because the studies had involved a nonhigh-risk fracture population. This is particularly true for the incidence of nonvertebral fractures, where the therapeutic effect is masked by a greater proportion of true traumatic fractures than for vertebral fractures. Therefore, it is becoming increasingly important to include further sources of evidence (**Figure 1**), for example, from meta-analyses of randomized controlled trials and indirect evidence from surrogate endpoints for fracture. Finally, observational database studies comparing ibandronate to other N-BPs are reviewed, also in terms of fracture incidence, as would never be obtained from unlikely "head-to-head" clinical trials.

Here, we review the antifracture efficacy of ibandronate over time, which at marketed doses of 150 mg once monthly oral and at 3 mg quarterly intravenous (i.v.), is licensed for the treatment of postmenopausal osteoporosis. A literature search was carried out using the PubMed online scientific citation database of published, peer-reviewed manuscripts up to and including December 2012. The keywords used for the literature search were ibandronate, osteoporosis, fracture, bone mineral density, and bone turnover marker (BTM). To meet the inclusion criteria, manuscripts had to be primary, peer-reviewed publications, in English, which reported either fracture endpoints or surrogate marker endpoints. The results were then further assessed to include only Phase III clinical trials, meta-analyses, or observational studies. Finally, observational database studies comparing ibandronate to other N-BPS were reviewed. The literature search results were supplemented with any study data that was known to the authors.

2. Pharmacologic profile of ibandronate

Bisphosphonates are stable synthetic analogs of pyrophosphate with a P–C–P backbone that binds avidly to hydroxyapatite on the bone surface. The presence of a nitrogen atom on either of the two covalently attached side chains generally separates bisphosphonates into two classes, non-nitrogen- and nitrogen-containing bisphosphonates. N-BPs such as ibandronate are significantly more potent bone resorption inhibitors than the non-nitrogen agents such as clodronate. Following uptake by osteoclasts, non-N-BPs are metabolized to analogs of ATP, leading to osteoclast apoptosis. N-BPs principally inhibit farnesyl diphosphate synthase (FDPS) in the mevalonate pathway causing inhibition of important intermediates required for the prenylation of signaling GTPases, ultimately resulting in osteoclast dysfunction and apoptosis.

Inhibition of FDPS also causes an accumulation of isopentenyl diphosphate (IPP), which is metabolized to an intracellular ATP analog, that inhibits mitochondrial ADP/ATP translocase, causing loss of mitochondrial membrane potential and direct induction of osteoclast apoptosis. Accumulation of IPP, activating γδ T-cells, also contributes to the acute-phase reaction (APR) that is commonly observed following the first infusion of a N-BPs, such as ibandronic acid. Recently, we found that the number of circulating γδ T cells, together with age, are important determinants of the occurrence of APR after intravenous infusion of nitrogen-containing bisphosphonates [8], and that desensitization leading to the occurrence of the APR in patients previously treated with N-BPs is because of a long-lasting reduction in the number of circulating γδ T cells [9]. The potency of ibandronate is because of its structural attributes (**Box 1**), with the addition of a tertiary nitrogen group on the R2 side chain, making the drug 2-, 50-, and 500-fold more potent than alendronate, pamidronate, and clodronate, respectively [10]. This increased potency, together with the strong binding affinity of ibandronate with the mineral component of bone (which is greater than that of clodronate or risedronate, even if lower than alendronate and zoledronate) [11], and its extended persistence in skeletal tissue, allows monthly or quarterly administration of ibandronate [12-14].

3. Evidence from antifracture randomized controlled clinical trials

Two randomized, controlled, antifracture trials have been carried out for ibandronate: The BONE (oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe)

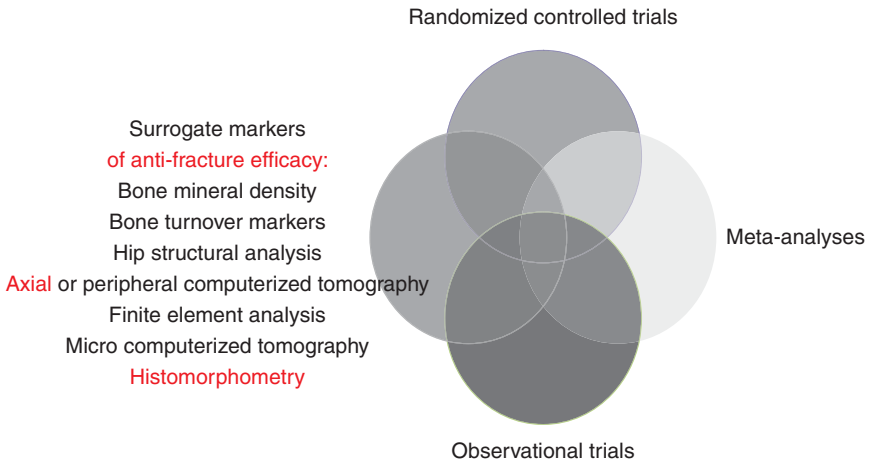


Figure 1. Sources of direct and indirect evidence of anti-fracture efficacy.

study, involving an oral ibandronate regimen administered daily (2.5 mg) or intermittently (20 mg every other day for 12 doses every 3 months) for 3 years [3] and the fracture prevention study, of an i.v. ibandronate regimen (0.5 and 1.0 mg every 3 months) for 3 years [15]. In the IV fracture prevention study, the cumulative incidence of new vertebral fractures with both 0.5 and 1 mg i.v. ibandronate once every 3 months was lower than that observed with the placebo at the end of 3 years, but the magnitude of the reduction of relative risk (RRR) did not attain statistical significance in the intention to treat (ITT) analysis [15]. In the per-protocol (PP) population, the RRR with 1 mg i.v. ibandronate (26%) approached statistical significance ($p = 0.0549$). The Intermittent Regimen Intravenous Ibandronate Study (IRIS) showed that a higher (2 mg i.v.) ibandronate dose once every 3 months provided greater substantial increases in Bone Mineral Density (BMD) than a 1 mg dose (increase in lumbar spine BMD from baseline of 5.0 vs. 2.8%, respectively) [16]. Therefore, the authors concluded that the dose of ibandronate used in the IV fracture prevention study (0.5 and 1.0 mg every 3 months) was suboptimal. The sustained efficacy of a daily oral ibandronate regimen to reduce the incidence of vertebral fractures was demonstrated in BONE, a Phase III clinical trial in which vertebral fracture risk reduction was the primary endpoint [3,17]. After the first year of treatment, the RRR in ITT analysis of a new vertebral fracture was 58% ($p = 0.0561$; ITT population) with a 2.5 mg daily oral dose of ibandronate compared with placebo. This RRR was sustained over 3 years of treatment (year 3: 62% $p = 0.0001$), indicating that ibandronate sustained considerable vertebral antifracture efficacy over time [18]. Interestingly, this was also the first trial to demonstrate vertebral antifracture efficacy of an intermittent regimen (20 mg every other day for 12 doses every 3 months), with a RRR of new vertebral fracture of 56% ($p = 0.0017$) and 50% ($p = 0.0006$) over 2 and 3 years, respectively. A *post hoc* analysis of data from the BONE study showed that daily ibandronate also has a significant and sustained effect on the incidence of new moderate or severe vertebral fractures [19]: the relative risk was reduced by 59% at years 1, 2, and 3. In BONE, nonvertebral fracture risk reduction was demonstrated in a *post hoc* subgroup analysis of high-risk patients with a baseline femoral neck BMD *T*-score < 3.0 (RRR 69%, $p = 0.013$ [3] or < 2.5 and a history of clinical fracture in the past 5 years (RRR 60%, $p = 0.037$) [20]. In the overall BONE study population, there was no statistically significant reduction in the risk of nonvertebral fracture between ibandronate treatment and calcium and vitamin D supplementation alone, although this was not the primary endpoint of the trial, the study was not designed or powered to demonstrate an effect at nonvertebral sites. The patient population in the BONE study was at relatively low risk for new nonvertebral fractures, with a relatively high mean BMD at the total hip at baseline (mean *T*-score = 1.73). Various randomized controlled trials for the treatment of postmenopausal osteoporosis with the oral bisphosphonates alendronate [1,21] and risedronate [22] have reported reductions in nonvertebral fractures; however, they were not significant. Unlike vertebral fractures, nonvertebral fractures generally occur as a result of external trauma. Therefore, the nonvertebral fracture risk of the patient cannot be considered as the only predictor of the osteoporotic condition [23]. External factors are unlikely to be modified by treatment and may become more important if the patient population recruited into a study is not at a high risk of fracture [23,24].

4. Evidence through meta-analyses

Two meta-analyses of ibandronate trials have demonstrated efficacy even on nonvertebral fracture, if given in proper doses [25,26]. Of note, these were analyses of individual patient data rather than the mean values reported in each study, thus increasing the validity of the analyses.This was achieved by merging patient data into Annual Cumulative Exposition (ACE) groups, based on a mean absorption rate of 0.6% for

oral dosing [27], and 100% for i.v. dosing (ACE = single dose × number of doses/year × absorption rate). Overall, licensed ibandronate doses were grouped into ACE categories equal to 5.5 mg (2.5 mg daily) and 10.8 mg (including 150 mg once monthly, 3 mg quarterly i.v. and 2 mg every 2 months i.v.); the effects of which have been compared to the ones in the placebo group (ACE = 0) or between them. Ibandronate, at the licensed oral and i.v. doses versus calcium and vitamin D supplements, has proved to significantly reduce the relative risk of clinical fracture (RRR: 28.8%, 95% IC: 0.55 – 0.92%, p = 0,010), including vertebral fractures, and all nonvertebral fractures (RRR: 29.9%; 95% CI: 0.50 – 0.99%; p = 0.041), moreover those in the most clinical relevant sites (RRR: 34.4%; 95% CI: 0.45 – 0.96%; p = 0.032) [26]. A comparison was made for the first time between two different drug doses: ibandronate doses equivalent to 150 mg oral monthly or 3 mg i.v. quarterly has been associated with a significant reduction in nonvertebral fracture incidence (RRR 38%; IC95%: 0.40 – 0.97%; p = 0,038), compared to the dose of 2.5 mg oral daily that had already proved to decrease vertebral fracture incidence [25].

5. Evidence from surrogate endpoints

A statistically significant linear relationship between BMD changes at the spine and hip and RRR in nonvertebral fracture was shown in a meta-analysis of controlled trials [28]. Individual trials have also demonstrated the correlation between BMD changes and antifracture efficacy: analysis from the Fracture Intervention Trial (FIT) showed that patients who had ≥ 3% increases in total hip BMD after 12 months of alendronate therapy were at the lowest risk of new vertebral fracture (3.2 vs. 6.3% of patients whose BMD levels remained stable or declined [29]. Ibandronate studies data analysis that exhibited densitometric effect comparable to alendronate treatment [30], also proved a similar result on the correlation between BMD increment and fracture risk reduction [16,31]. Although there is evidence, probably because of limited precision of the densitometry or BMD unrelated bone effects, even with decrease or no change in BMD value there could be a reduction in fracture risk [32,33], it is also true that patients who display an increase of BMD have a higher reduction of fracture risk. Recently, a meta-analysis of spine BMD dose–response relationships for alendronate, risedronate, and ibandronate was performed [34]. All three nitrogen-containing bisphosphonates were approximately equipotent and exhibited a log-linear relationship between dose and the increase in spine BMD. Differences in efficacy between the available bisphosphonate regimens appear to be a function of dose rather than to inherent differences in their respective therapeutic potential. Reductions in BTMs are also regarded as valid surrogate endpoints for antifracture efficacy. A relationship between reductions in BTMs and fracture incidences has also been reported: as BTM decreases, fracture incidence decreases [28,35,36]. Overall, a 70% reduction in bone resorption markers and a 50% reduction in bone formation markers significantly reduced the nonvertebral fracture risk by 40% [28]. A reduction of 30% in BMT is sufficient to cause a significant decrease in vertebral fracture risk. The decrease has to be over 50% to have an effect on nonvertebral fracture incidence, reflecting the effect on cortical bone, which is less responsive to treatment (**Figure 2**). In the BONE study, both the daily and intermittent ibandronate regimens provided a pronounced reduction in median urinary c-telopeptide of type I collagen (CTX) levels relative to baseline within 3 months of administration (58.9 and 49.2%, respectively). These median reductions from baseline were sustained throughout the 3-year study (65.3 and 52.7%, respectively; p < 0.0001 for both regimens versus calcium and vitamin D supplement only). In the studies using lower doses of ibandronate (0.5 and 1 mg e.v.), which later turned out to be insufficient, the incidence of new vertebral fractures was lower than placebo at 3 years, but this did not reach statistical significance [15]. This is associated with small elevation in mean lumbar spine BMD (0.5 mg, 3.9%; 1 mg, 4.9%) and reductions in median urinary CTX (0.5 mg, 41.4%; 1 mg, 45.0%) relative to baseline. A significant CTX reduction, over 50% within 3 days from administration, has been observed with the licensed higher doses of ibandronate [37]. CTX level variations after 3 months of ibandronate treatment proved to be predictive in almost all patients of lumbar BMD increase at 1-year [38]. It is important to underline that a reduction greater than 50% in CTX level, persistent during the study years and index of vertebral and nonvertebral fracture prevention, has occurred in more patients using the current monthly or quarterly doses instead of the 2.5 mg daily dose [39].

New techniques evaluating bone strength surrogate markers are available currently. Some can better describe densitometric variations in different sites, others express bone geometrical features correlated to fracture risk independently from densitometry. An increase of volumetric BMD at vertebral edge and at trabecular and subcortical femoral regions has been observed with computerized tomography, either axial or peripheral (pQCT), after treatment with oral ibandronate [40]. Moreover, studies documented an increase in strength indices by pQCT, Finite Element Analysis, and hip structural analysis [41,42], or an improved cortical BMD at the tibia by high-resolution pQCT [43]. Ibandronate's positive effects on trabecular bone microarchitecture has been observed with microCT [44,45] and histomorphometry [46,47].

6. Bridging trials

In case a drug has already demonstrated antifracture efficacy in a randomized, controlled trial authorities such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) suggest the use of "bridging studies" using surrogate endpoints for fracture for the approval of new dosing regimens or routes of administration [48]. Bridging studies, with BMD changes as their primary endpoint and

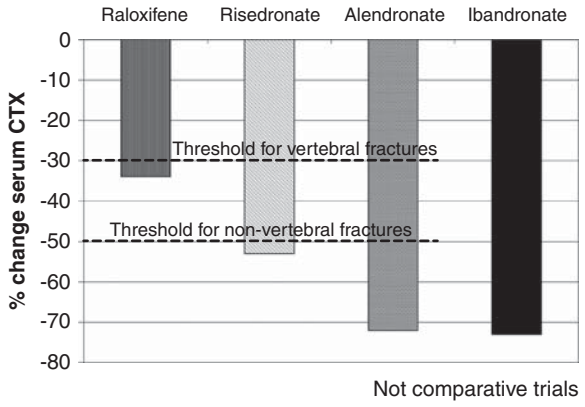


Figure 2. A reduction of 30% in BMT is sufficient to cause a significant decrease in vertebral fracture risk. The decrease has to be over 50% to have an effect on nonvertebral fracture incidence than reflect effect on cortical bone, less responsive to treatment. A significant serum CTX reduction, over 50% within 3 days from administration, has been observed with the licensed doses of ibandronate.

BTM changes as their secondary endpoint, have led to the approval of 70 mg weekly alendronate and 35 mg weekly risedronate regimens [49,50]. A monthly dosing of 75 mg risedronate on two consecutive days a month (5 mg daily 30 days 150 mg) was also approved in 2008 based on data from a bridging trial [51]. Changes in BMD and BTMs have been widely used as surrogate markers for antifracture efficacy with different ibandronate regimens [52-56]. Ibandronate at doses of 150 mg oral once monthly (double the equivalent of the daily dose, 2.5 mg daily × 30 = 75 mg) and 3 mg quarterly i.v. were also approved based on results from two bridging studies, the MOBILE (Monthly Oral iBandronate In LadiEs) study [55,56] and the Dosing IntraVenous Administration (DIVA) study [52,54]. The MOBILE and DIVA studies demonstrate that both ibandronate oral once monthly and quarterly i.v. regimens are able to increase BMD and suppress BTMs to levels that are consistent with antifracture efficacy at vertebral and nonvertebral sites. In the MOBILE trial, after 1 year, lumbar spine BMD significantly increased from baseline by 4.9% with 150 mg once-monthly ibandronate versus 3.9% with daily 2.5 mg treatment [56]. This increment was sustained for 2 years, with an increase in lumbar spine BMD from baseline of 6.6% with 150 mg once monthly ibandronate versus 5.0% with daily treatment [55]. Similarly, ibandronate 3 mg quarterly i.v. was shown to increase BMD significantly > 2.5 mg oral daily in the DIVA study [52,54]: after 1 year, lumbar spine BMD increased from baseline by 4.8% with 3 mg quarterly i.v. ibandronate versus 3.8% with daily oral treatment [54]. This increase was sustained for 2 years (+ 6.3 vs. 4.8%) [52], at the end of which significant BMD increases at total hip and trochanter with 3 mg quarterly i.v. ibandronate were seen. Monthly oral and quarterly i.v. regimens were better also in terms of BTM associated with decrease in fracture risk: serum CTX was markedly reduced from baseline after 3 months (> 50% change from baseline) and this change was sustained throughout the 2-year study [52,54-56]. Furthermore, the proportion of patients reporting a > 50% reduction in serum CTX from baseline was significantly higher with the once-monthly dose versus daily dosing after 2 years, with a greater antifracture effect ($p = 0.002$) [39].

7. Long-term extension studies

In a chronic disease such as osteoporosis, it is important to test the efficacy of the treatment also in the long-term scenario. In the MOBILE Long Term (MOBILE LTE) study, patients from MOBILE who received either ibandronate 100 mg monthly or 150 mg monthly continued on the same treatment for another 3 years. In the extension study, oral 150 mg ibandronate showed sustained efficacy in lumbar spine BMD with an increase from baseline of 7.8% at 4 years to 8.4% at 5 years [20,57]. BMD gains at the total hip, femoral neck, and trochanter, achieved during the 2-year MOBILE study, were generally maintained during the extension study [57] (BMD total hip + 3.5%, femoral neck + 3.2%, and trochanter + 6.0%). A rapid and significant decrease of BTM (CTX) from baseline was noticed during the first 3 months of treatment which was sustained > 50% over 5 years of 150 mg once monthly ibandronate therapy [58], indicating a sign of antifracture efficacy. Similar to P1NP, a marker of new bone formation, that reached its nadir after 12 months of treatment and remained stable during the study years, proving the absence of a deleterious cumulative effect of the treatment [58]. In terms of absolute changes in BTM, in contrast with the results of the study with suboptimal doses of ibandronate [15], the BTM decrease described in MOBILE (with the adequate licensed doses) shows evidence for reductions to the "premenopausal" normal reference range [59]. In the DIVA Long TErm study, patients from DIVA who received either i.v. ibandronate 2 mg every 2 months or 3 mg every 3 months continued on the same treatment for 5 years, and similar data were observed [60].

8. Observational studies

Owing to the requirement of large sample sizes, any direct comparative clinical trial of antifracture efficacy is unrealistic. Observational studies offer one possibility of overcoming this hurdle, if well designed. Data regarding the use of osteoporotic drugs and the incidence of clinical fractures can be collected and analyzed from medical claims databases, derived from insurance companies. They offer a real-world clinical perspective into the effects of different bisphosphonate regimens, outside the confines of a controlled clinical trial with their strict inclusion and exclusion criteria [61]. However, because of the lack of randomization and disregard to patients features (i.e., baseline BMD), observational studies are subject to potential bias and confounding, which can be reduced but

not fully eliminated by appropriate statistical methods. A 12-month observational study, VIBE (The eValuation of IBandronate Efficacy database fracture study), comparing the risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates (alendronate and risedronate), was carried out in patients from two US-based databases [62]. In > 64,000 patients, the incidence of any clinical fracture was significantly lower (p = 0.052) in patients receiving ibandronate therapy compared with patients on weekly bisphosphonates (adjusted relative risk: 0.82, 95% CI: 0.66 – 1.00%). The incidence of vertebral fracture was significantly lower in patients receiving ibandronate compared with patients on weekly bisphosphonates (adjusted relative risk: 0.36, 95% CI: 0.18 – 0.75%; p = 0.006). The RRR in nonvertebral and hip fractures was comparable among the monthly and weekly bisphosphonates.

9. Experiences in osteoporosis other than postmenopausal

Some studies are available on the effects of ibandronate, in terms of BMD, in some forms of secondary osteoporosis or in particular to men. In 2003, patients with glucocorticoid-induced osteoporosis treated with ibandronate 2 mg quarterly were reported to demonstrate a significant BMD improvement, a decrease in back pain, and a progressive reduction in new vertebral fracture risk [63]. An improvement in cortical BMD measured with pQCT was also observed in SLE patients receiving 150 mg oral monthly ibandronate [64]. Results of an RCT with 150 mg oral monthly ibandronate versus placebo aiming to verify efficacy and safety in males with low BMD have recently been published [65]. After 1 year, in ITT analysis, ibandronate proved to increase BMD, both at lumbar spine (+ 3.5%) and proximal femoral epiphysis (+ 1.8%), significantly higher than in calcium–vitamin D supplementation. Among males who have completed the study with a good adherence to the treatment, it has exhibited a good tolerability and a greater decrease in BTMs. In addition, ibandronate treatment also proved to be effective in bone loss and fracture prevention in heart- and liver-transplanted patients [66,67].

10. Treatment adherence

Adherence is fundamental for clinical effectiveness of any treatment. Among treatments with the same efficacy, safety profiles, and cost, the one that guarantees the best adherence, especially in the long term is most preferred. A treatment course shorter than 6 months as demonstrated through an observational study was found to have no effect on fracture risk [68]. The fracture risk decreases only with an adherence > 50%, over this value fracture risk declines in an exponential trend [69]. It has been reported that about half of the patients discontinue the daily oral osteoporosis therapy within the first year [70]; moreover, compliance is often insufficient for many reasons [71]. To overcome this kind of problem in clinical practice, new regimens have been developed for some drugs, such as bisphosphonates, with a pharmacokinetics that allows an intermittent administration. Intermittent oral treatment has produced the expected improvement in adherence to therapy [72]. However, compliance is still unsatisfactory even with weekly regimen [73]. Bisphosphonates licensed for osteoporosis treatment differ in their chemical, physical, and biological proprieties which in turn influence administration intervals [74]. Only the most powerful, as ibandronate and zoledronate, are eligible for an administration regimen less frequent than weekly. On the other hand, fracture risk reduction with intermittent regimen has been documented only for some molecules [2,3]. Persistence in bisphosphonates therapy after 1 year seems to be mostly related to the occurrence of gastro-enteric adverse events and administration interval [71,75,76]. A weekly dose is associated with better tolerability and adherence versus a daily dose [71,73], similarly there are studies reporting a better tolerability of monthly ibandronate versus weekly bisphosphonates [76,77]. A retrospective pharmaco-epidemiologic French study in a wide database made by a general practitioner underlines a minor risk of treatment discontinuation and better compliance with the monthly dose compared to the weekly bisphosphonates: patients receiving oral monthly ibandronate showed a discontinuation rate minor than patients with weekly bisphosphonates by 37% [78]. A similar database in Italy has been recently used to compare persistence and compliance of weekly or monthly bisphosphonates with daily administration of strontium ranelate [79,80]. Patients taking weekly risedronate have an increased risk of treatment discontinuation after first prescription compared to ibandronate (OR 1.43; 95% CI 1.36 – 1.49); this risk was more than double in patients with strontium ranelate. Moreover, risedronate and strontium ranelate compared to ibandronate had a risk of low compliance increased by two and three times, respectively. These results reveal that monthly ibandronate in Italian clinical practice guarantees better adherence, either in terms of compliance and persistence, than weekly risedronate and especially daily strontium ranelate. Thus, it could attribute to a greater effect on osteoporotic fracture risk reduction and probably a better pharmaco-economic profile. In our opinion, the good results from MOBILE [55] and MOBILE LTE [57] with the lower dose of 100 mg ibandronate monthly (equivalent to a MPR = 67% of 150 mg dose) should be considered, as they give further evidence of ibandronate efficacy even in low-compliance condition, quite common in real-life practice.

In conclusion, the treatment with ibandronate appears better than other pharmacological approaches in terms of adherence and effectiveness.

11. Safety profile and tolerability of ibandronate compared to other BPs

Clinical trials reported no differences in gastrointestinal adverse events between BPs and placebo [81]. Nevertheless,

gastrointestinal side effects are commonly caused on discontinuation of daily or weekly bisphosphonates [71,82]. This could be explained by many factors such as improper administration procedure, concomitant gastrointestinal diseases, or just the fear of adverse events. In Italian population, poor compliance has been observed in patients undergoing treatment with gastroprotective drugs [71]. In clinical trials on ibandronate [3,55], there was no difference in gastrointestinal adverse events between the study groups, even if patient with concomitant gastrointestinal discomforts or taking NSAID or anti-ulcer drugs, common in patients with vertebral fracture [83], were not excluded. Moreover, reducing the frequency of contact of bisphosphonates with upper gastrointestinal way with weekly or monthly regimen should lead to a decrease in relevant gastrointestinal adverse events. The potential increase of gastrointestinal events because of a higher monthly dose could be balanced by a reduction in administration frequency. In fact it has been observed that expanding the administration interval, thanks to monthly ibandronate, results in a better adherence in patients who had discontinued oral daily or weekly bisphosphonates because of poor gastrointestinal tolerability [76,84]. There are other studies reporting a better compliance and a minor frequency in gastrointestinal side effects with weekly vs daily regimen [85] or monthly vs weekly [76,86]. Thus, monthly bisphosphonate treatment should be preferred in patients at high risk of gastrointestinal adverse events or taking several drugs, frequent conditions in elder people in whom a good tolerability has been confirmed [87]. In patients with overt contraindication or gastrointestinal diseases, parenteral administration of bisphosphonates is recommended.

So, i.v. bisphosphonates have a slight risk of renal toxicity that could be reduced by appropriate hydration and infusion time. Both ibandronate and zoledronate have a good renal safety profile in postmenopausal women with glomerular filtration rate (GFR) > 30 ml/min [88,89]. The lack of head-to-head trials in osteoporotic patients makes a comparison also in terms of safety [90] impossible. Ibandronate was found to be safer than zoledronate in patients treated for myeloma [91]. Furthermore, there are evidence of ibandronate's lack of renal toxicity in patients with impaired renal function earlier to the first administration [92,93]. These aspects could be explained by the different pharmacokinetic features of ibandronate [94]: compared to pamidronate and zoledronate, ibandronate has higher protein binding rate (87%) that could reduce renal exposure to free circulating drug; moreover, ibandronate tissue half-life is much shorter than zoledronate (24 days vs 150 – 200 days, respectively). I.v. ibandronate might be preferable to zoledronate in patients with chronic renal failure or at high risk of renal toxicity because of concomitant medications. However, patients with renal function impairment should be investigated for osteomalacia or a dynamic bone disease before bisphosphonate administration and the dose adjusted for GFR [90]. The Designed for i.v. Ibandronate reNal safety Evaluation (DIVINE) study was a 1-year prospective, randomized, open label, multi-center study that evaluated the renal safety of quarterly (every 3 months) ibandronate i.v. injection given over 15 – 30 s compared with infusion given over 15 min in women with postmenopausal osteoporosis at increased risk for renal disease [95]. The results of this study demonstrate the profile of i.v. ibandronate, which allows it to be dosed as an i.v. injection in the primary care setting without the need for an infusion, even in patients with pre-existing hypertension or diabetes mellitus. In conclusion, among the N-BPs, there are evidence of a better gastrointestinal and renal tolerability profile for oral and i.v. ibandronate administration, respectively. Recently, arisen safety issues of long-term bisphosphonate treatment, attributed to extended oversuppression of bone turnover, are the risk of osteonecrosis of the jaw (ONJ) and atypical fractures. In a recent review, 88% of ONJ cases were associated with intravenous therapy, primarily zoledronate, and only 11% had received oral bisphosphonates, in most cases alendronate [96]. Only few case reports of ONJ have been reported with the use of ibandronate. The lower binding affinity of ibandronate with the mineral component of bone in comparison to zoledronate or alendronate [11], might potentially be associated with lower risk of both ONJ and atypical fractures.

12. Conclusions

In the evaluation of any treatment, the whole body of evidence should be considered. A large amount of data from randomized, controlled fracture trials, bridging studies using surrogate endpoints, meta-analyses, and observational studies based on a clinical setting is available to suggest that ibandronate has sustained vertebral and nonvertebral antifracture efficacies in women with postmenopausal osteoporosis.

13. Expert opinion

The purpose of pharmacologic treatment of osteoporosis is to reduce the risk of fractures, both vertebral and nonvertebral. The most reliable way of gathering evidence of antifracture efficacy is directly from randomized placebo-controlled clinical trials, which contain large patient cohorts and are designed specifically to control the potential biases. Pivotal studies on ibandronic acid efficacy in terms of antifracture effects on nonvertebral fractures had some intrinsic limitations with respect to the inclusion criteria for ethical reasons of a low-risk population. This is particularly true in case of nonvertebral fractures, where the therapeutic effect is masked by a greater proportion of traumatic fractures than for vertebral fractures. Nevertheless, additional evidence of efficacy is available from meta-analyses of randomized controlled trials and from surrogate endpoints for fractures. This large body of evidence suggests that ibandronate has sustained vertebral and nonvertebral anti-fracture efficacies in women with postmenopausal osteoporosis comparable to those observed with other N-BPs. Differences in efficacy between the available

bisphosphonate regimens appear to be a function of dose rather than inherent differences in their therapeutic potential.

Efficacy in the clinical practice (effectiveness) may be compromised by poor treatment compliance and/or failure to persist with the prescribed treatment. Drugs or treatment regimens that reduce the risk for osteoporotic fractures and make the treatment of osteoporosis more convenient and suitable for patients are preferred: ibandronic acid at marketed doses of 150 mg once monthly oral and 3 mg quarterly i.v. injection, given over 15 – 30 s, has these characteristics. The robust results observed even with the lower oral dose of 100 mg monthly should be considered: they give further warranty when a suboptimal compliance is expected, which is quite common in real-life practice.

A notable progress in the pharmacological treatment of osteoporosis over the last two decades has been achieved, such that patients with skeletal fragility now have a variety of effective therapeutic choices that may be tailored to individual preferences. Other factors such as improved therapeutic adherence and/or a better safety profile now play a greater role in the medication choice. Among N-BPs, there are evidence of a better gastrointestinal and renal tolerability profile for oral and i.v. ibandronate administration, respectively.

The main advantages of ibandronate over other bisphosphonates appear to be the lower effective dose and the intermittent i.v. administration. These apply also for zoledronate, but its effects extended for years might be a reason of concern in some conditions.

In the last few years, the issue about treatment duration has gained considerable importance. The antifracture effect of antiresorptive agents such as bisphosphonates is based on the suppression of turnover "per se," which reverts after treatment discontinuation at different lag times. Ibandronate, at variance with alendronate or zoledronate, is characterized by an earlier return of BTMs to normal values after treatment discontinuation. [97]. This obviously limits the possibility of "drug holiday", but it might be considered a remarkable advantage when, for example, patients develop conditions associated with a greater risk of ONJ, such as an invasive dental intervention [98]. For the same reason, ibandronate might be preferable for sequential osteoporosis treatments with teriparatide, which seem to work better if bone turnover is not fully suppressed [99].

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535-41
2. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22
3. Chesnut CH, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004;19:1241-9

• **Pivotal trial.**

4. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. J Am Med Assoc 1999;282:1344-52
5. Sambrook P, Cooper C. Osteoporosis. Lancet 2006;367:2010-18
6. Brody BA, Dickey N, Ellenberg SS, et al. Is the use of placebo controls ethically permissible in clinical trials of agents intended to reduce fractures in osteoporosis? J Bone Miner Res 2003;18:1105-9
7. Temple RJ. Study designs in osteoporosis. J Bone Miner Res 2003;18:1129-32
8. Rossini M, Adami S, Viapiana O, et al. Circulating γ, δ T cells and the risk of acute-phase response after zoledronic acid administration. J Bone Miner Res 2012;27:227-30
9. Rossini M, Adami S, Viapiana O, et al. Long-term effects of amino-bisphosphonates on circulating γ, δ T cells. Calcif Tissue Int 2012;91:395-9
10. Muhlbauer RC, Bauss F, Schenk R, et al. BM 21.0955, a potent new bisphosphonate to inhibit bone resorption. J Bone Miner Res 1991;6:1003-11
11. Nancollas GH, Tang R, Phipps RJ, et al. Novel insights into actions of bisphosphonates on bone: differences in interactions with hydroxyapatite. Bone 2006;38:617-27
12. Monier-Faugere MC, Geng Z, Paschalis EP, et al. Intermittent and continuous administration of the bisphosphonate ibandronate in ovariohysterectomized beagle dogs: effects on bone morphometry and mineral properties. Bone Miner Res. 1999;14:1768-78
13. Muller R, Hannan M, Smith SY, et al. Intermittent ibandronate preserves bone quality and bone strength in the lumbar spine after 16 months of treatment in the ovariectomized cynomolgus monkey. J Bone Miner Res 2004;19:1787-96
14. Smith SY, Recker RR, Hannan M, et al. Intermittent intravenous administration of the bisphosphonate ibandronate prevents bone loss and maintains bone strength and quality in ovariectomized cynomolgus monkeys. Bone 2003;32:45-55
15. Recker R, Stakkestad JA, Chesnut CH, et al. Insufficiently dosed intravenous ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. Bone 2004;34:890-9

• **Pivotal trial.**

16. Adami S, Felsenberg D, Christiansen C, et al. Efficacy and safety of ibandronate

given by intravenous injection once every 3 months. Bone 2004;34:881-9

17. Chesnut CH, Ettinger MP, Miller PD, et al. Ibandronate produces significant, similar antifracture efficacy in North American and European women: new clinical findings from BONE. Curr Med Res Opin 2005;21:391-401
- **Pivotal trial.**

18. Brandi ML. Sustained vertebral antifracture efficacy of oral anti-osteoporotic therapies in postmenopausal osteoporosis. Curr Med Res Opin 2010;26:2553-63

19. Felsenberg D, Miller P, Armbrecht G, et al. Oral ibandronate significantly reduces the risk of vertebral fractures of greater severity after 1, 2, and 3 years in postmenopausal women with osteoporosis. Bone 2005;37:651-4
- **Pivotal trial.**

20. Epstein S, Jeglitsch M, McCloskey E. Update on monthly oral bisphosphonate therapy for the treatment of osteoporosis: focus on ibandronate 150 mg and risedronate 150 mg. Curr Med Res Opin 2009;25:2951-60

21. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the fracture intervention trial. JAMA 1998;280:2077-82

22. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11:83-91

23. Rossini M, Viapiana O, Gatti D, et al. Once-monthly oral ibandronate in postmenopausal osteoporosis: translation and updated review. Clin Ther 2009;31:1497-510

24. Sebba A. Comparing non-vertebral fracture risk reduction with osteoporosis therapies: looking beneath the surface. Osteoporos Int 2009;20:675-86

25. Cranney A, Wells GA, Yetisir E, et al. Ibandronate for the prevention of nonvertebral fractures: a pooled analysis of individual patient data. Osteoporos Int 2009;20:291-7
- **Meta-analysis.**

26. Harris ST, Blumentals WA, Miller PD. Ibandronate and the risk of non-vertebral and clinical fractures in women with postmenopausal osteoporosis: results of a meta-analysis of phase III studies. Curr Med Res Opin 2008;24:237-45
- **Meta-analysis.**

27. Barrett J, Worth E, Bauss F. Ibandronate: a clinical pharmacological and pharmacokinetic update. J Clin Pharmacol 2004;44:951-65

28. Hochberg MC, Greenspan S, Wasnich RD, et al. Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. J Clin Endocrinal Metab 2002;87:1586-92

29. Hochberg MC, Ross PD, Black D, et al. Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. Fracture Intervention Trial Research Group. Arth Rheum 1999;42:1246-54

30. Miller PD, Epstein S, Sedarati F, et al. Once-monthly oral ibandronate compared with weekly oral alendronate in postmenopausal osteoporosis: results from the head-to-head MOTION study. Curr Med Res Opin 2008;24:207-13

31. Miller PD, Delmas PD, Huss H, et al. Increases in hip and spine bone mineral density are predictive for vertebral antifracture efficacy with ibandronate. Calcif Tissue Int 2010;87:305-13

32. Cummings SR, Karpf DB, Harris F, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. Am J Med 2002;112:281-9

33. Wasnich R, Miller P. Antifracture efficacy of antiresorptive agents are related to changes in bone density. J Clin End Metab 2000;85:231-2

34. Yates J. A meta-analysis characterizing the dose-response relationships for three oral nitrogen-containing bisphosphonates in postmenopausal women. Osteoporos Int 2013;24:253-62

35. Bauer DC, Black DM, Garnero P, et al. Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the fracture intervention trial. J Bone Miner Res 2004;19:1250-8

36. Eastell R, Barton I, Hannon RA, et al. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. J Bone Miner Res 2003;18:1051-6

37. Binkley N, Silverman SL, Simoncelli C, et al. Monthly ibandronate suppresses serum CTX-I within 3 days and maintains a monthly fluctuating pattern of suppression. Osteoporos Int 2009;20:1595-601

38. Hochberg MC, Silverman SL, Barr CE, et al. The utility of changes in serum levels of C-terminal telopeptide of type I collagen in predicting patient response to oral monthly ibandronate therapy. J Clin Densitom 2010;13:181-9

39. Rossini M, Idolazzi L, Adami S. Evidence of sustained vertebral and non vertebral antifracture efficacy with ibandronate therapy: a systematic review. Ther Adv Muskuloskel Dis 2011;3:67-79

40. Engelke K, Fuerst T, Dasic G, et al. Regional distribution of spine and hip QCT BMD responses after one year of once-monthly ibandronate in postmenopausal osteoporosis. Bone 2010;46:1626-32

41. Lewiecki EM, Keaveny TM, Kopperdahl DL, et al. Once-monthly oral ibandronate improves biomechanical determinants of bone strength in women with postmenopausal osteoporosis. J Clin Endocrinol Metab 2009;94:171-80

42. Genant HK, Lewiecki EM, Fuerst T, et al. Effect of monthly ibandronate on hip structural geometry in men with low bone density. Osteoporos Int 2012;23:257-65

43. Chapurlat RD, Laroche M, Thomas T, et al. Effect of oral monthly ibandronate on bone microarchitecture in women with osteopenia-a randomized placebo-controlled trial. Osteoporos Int 2013;24:311-20

44. Recker RR, Ste-Marie LG, Langdahl B, et al. Oral ibandronate preserves trabecular microarchitecture: micro-computed tomography findings from the oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe study. J Clin Densitom 2009;12:71-6

45. Bock O, Börst H, Beller G, et al. Impact of oral ibandronate 150 mg once monthly on bone structure and density in post-menopausal osteoporosis or

osteopenia derived from in vivo muCT. Bone 2012;50:317-24

46. Recker RR, Ste-Marie LG, Langdahl B, et al. Effects of intermittent intravenous ibandronate injections on bone quality and micro-architecture in women with postmenopausal osteoporosis: the DIVA study. Bone 2010;46:660-5
47. Bala Y, Kohles J, Recker RR, et al. Oral ibandronate in postmenopausal osteoporotic women alters micromechanical properties independently of changes in mineralization. Calcif Tissue Int 2013;92:6-14
48. European Medicines Agency. Guideline on the Evaluation of New Medicinal Products in the Treatment of Osteoporosis. 2005. Available from: http://www.emea.eu.int/pdfs/human/ewp/055295en.pdf
49. Rizzoli R, Greenspan SL, Bone G, et al. Two-year results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis. J Bone Miner Res 2002;17:1988-96
50. Brown JP, Kendler DL, McClung MR, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int 2002;71:103-11
51. Delmas PD, Benhamou CL, Man Z, et al. Monthly dosing of 75 mg risendronate on 2 consecutive days a month: efficacy and safety results. Osteoporosis Int 2008;19:1039-45
52. Eisman JA, Civitelli R, Adami S, et al. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. J Rheumatol 2008;35:488-97
- **Pivotal trial.**
53. Adami S, Miller PD, Patel K, et al. Ibandronate induced bone mineral density gains are related to vertebral antifracture efficacy [abstract P034-T]. Calcif Tissue Int 2007;80(Suppl 1):s46
54. Delmas PD, Adami S, Strugala C, et al. Intravenous ibandronate injections in postmenopausal osteoporosis: 1-year findings from the DIVA study. Arthritis Rheum 2006;54:1838-46
- **Pivotal trial.**
55. Reginster JY, Adami S, Lakatos P, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Ann Rheum Dis 2006;65:654-61
- **Pivotal trial.**
56. Miller PD, McClung MR, Macovei L, et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. J Bone Miner Res 2005;20:1315-22
- **Pivotal trial.**
57. Miller PD, Recker RR, Reginster JY, et al. Efficacy of monthly oral ibandronate is sustained over 5 years: the MOBILE long-term extension study. Osteoporos Int 2012;23:1747-56
58. Felsenberg D, Recker RR, Kenwright A, et al. Suppression of bone turnover markers with monthly oral ibandronate is sustained over 5 years: the MOBILE LTE study [abstract P477]. Osteoporosis Int 2010;21(Suppl 1):S194
59. Adami S, Bianchi G, Brandi ML, et al. BONTURNO study group. Determinants of bone turnover markers in healthy premenopausal women. Calcif Tissue Int 2008;82:341-7
60. Bianchi G, Czerwinski E, Kenwright A, et al. Long-term administration of quarterly IV ibandronate is effective and well tolerated in postmenopausal osteoporosis: 5-year data from the DIVA study long-term extension. Osteoporos Int 2012;23:1769-78
61. Silverman SL. Osteoporosis therapies: evidence from health-care databases and observational population studies. Calcif Tissue Int 2010;87:375-84
62. Harris ST, Reginster JY, Harley C, et al. Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: the eValuation of IBandronate Efficacy (VIBE) database fracture study. Bone 2009;44:758-65
- **Observational study.**
63. Ringe JD, Dorst A, Faber H, et al. Intermittent intravenous ibandronate injections reduce vertebral fracture risk in corticosteroid-induced osteoporosis: results from a long-term comparative study. Osteoporos Int 2003;14:801-7
64. Li EK, Zhu TY, Hung VY, et al. Ibandronate increases cortical bone density in patients with systemic lupus erythematosus on long-term glucocorticoid. Arthritis Res Ther 2010;12:R198
65. Orwoll ES, Binkley NC, Lewiecki EM, et al. Efficacy and safety of monthly ibandronate in men with low bone density. Bone 2010;46:970-6
66. Fahrleitner-Pammer A, Piswanger-Soelkner JC, Pieber TR, et al. Ibandronate prevents bone loss and reduces vertebral fracture risk in male cardiac transplant patients: a randomized double-blind, placebo-controlled trial. J Bone Miner Res 2009;24:1335-44
67. Kaemmerer D, Lehmann G, Wolf G, et al. Treatment of osteoporosis after liver transplantation with ibandronate. Transpl Int 2010;23:753-9
68. Gallagher AM, Rietbrock S, Olson M, et al. Fracture outcomes related to persistence and compliance with oral bisphosphonates. J Bone Miner Res 2008;23:1569-75
69. Siris ES, Harris ST, Rosen CJ, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc 2006;81:1013-22
70. Kothawala P, Badamgarav E, Ryu S, et al. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. Mayo Clin Proc 2007;82:1493-501
71. Rossini M, Bianchi G, Di Munno O, et al. Determinants of adherence to osteoporosis treatment in clinical practice. Osteoporos Int 2006;17:914-21
72. Recker RR, Gallagher R, MacCosbe PE. Effect of dosing frequency on bisphosphonate medication adherence in a large longitudinal cohort of women. Mayo Clin Proc 2005;80:856-61
73. Ettinger MP, Gallagher R, MacCosbe PE. Medication persistence with weekly versus daily doses of orally administered bisphosphonates. Endocr Pract 2006;12:522-8
74. Russell RG, Watts NB, Ebetino FH, et al. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int 2008;19:733-59
75. Penning-van Beest FJ, Goettsch WG, Erkens JA, et al. Determinants of persistence with bisphosphonates: a study un women with postmenopausal osteoporosis. Clin Ther 2006;28:236-42

76. Binkley N, Martens MG, Silverman SL, et al. Improved GI tolerability with monthly ibandronate in women previously using weekly bisphosphonates. South Med J 2009;102:486-92

77. Blumentals WA, Harris ST, Cole RE, et al. Risk of severe gastrointestinal events in women treated with monthly ibandronate or weekly alendronate and risedronate. Ann Pharmacother 2009;43:577-85

78. Cotte FE, Fardellone P, Mercier F, et al. Adherence to monthly and weekly oral bisphosphonates in women with osteoporosis. Osteoporos Int 2010;21:145-55

79. Gatti D, Rossini M, Viapiana O, et al. Adherence to oral osteoporosis treatment in the Italian clinical practice. Reumatismo 2010;62(Suppl):1-8

80. Rossini M, Di Munno O, Gatti D, et al. Optimizing bisphosphonate treatment outcomes in postmenopausal osteoporosis: review and Italian experience. Clin Exp Rheumatol 2011;29:728-35

81. Cryer B, Bauer DC. Oral bisphosphonates and upper gastrointestinal tract problems: what is the evidence? Mayo Clin Proc 2002;77:1031-43

82. Hamilton B, McCoy K, Taggart H. Tolerability and compliance with risedronate in clinical practice. Osteoporos Int 2003;14:259-62

83. Rossini M, Bertoldo F, Lovato R, et al. Use of nonsteroidal anti-inflammatory drugs in patients with vertebral osteoporotic fractures. Reumatismo 2002;54:340-3

84. Lewiecki EM, Babbitt AM, Piziak VK, et al. Adherence to and gastrointestinal tolerability of monthly oral or quarterly intravenous ibandronate therapy in women with previous intolerance to oral bisphosphonates: a 12-month, open-label, prospective evaluation. Clin Ther 2008;30:605-21

85. Zambon A, Baio G, Mazzaglia G, et al. Discontinuity and failures of therapy with bisphosphonates: joint assessment of predictors with multi-state models. Pharmacoepidemiol Drug Saf 2008;17:260-9

86. Dernan R, Kohles JD, Babbitt A. Gastrointestinal tolerability with ibandronate after previous weekly bisphosphonate treatment. Clin Int Aging 2009;4:357-65

87. Ettinger MP, Felsenberg D, Harris ST, et al. Safety and tolerability of oral daily and intermittent ibandronate are not influenced by age. J Rheumatol 2005;32:1968-74

88. Miller PD, Ward P, Pfister T, et al. Renal tolerability of intermittent intravenous ibandronate treatment for patients with postmenopausal osteoporosis: a review. Clin Exp Rheumatol 2008;26:1125-33

89. Boonen S, Sellmeyer DE, Lippuner K, et al. Renal safety of annual zoledronic acid infusions in osteoporotic postmenopausal women. Kidney Int 2008;74:641-8

90. Miller PD. The kidney and bisphosphonates. Bone 2011;49:77-81

91. Weide R, Koppler H, Antras L, et al. Renal toxicity in patients with multiple myeloma receiving zoledronic acid vs. ibandronate: a retrospective medical records review. J Cancer Res Ther 2010;6:31-5

92. Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. Kidney Int 2008;74:1385-93

93. Bergner R, Henrich DM, Hoffmann M, et al. Renal safety and pharmacokinetics of ibandronate in multiple myeloma patients with or without impaired renal function. J Clin Pharmacol 2007;47:942-50

94. Body JJ, Pfister T, Bauss F. Preclinical perspectives on bisphosphonate renal safety. Oncologist 2005;19(Suppl):3-7

95. Miller PD, Ragi-Eis S, Mautalen C, et al. Effects of intravenous ibandronate injection on renal function in women with postmenopausal osteoporosis at high risk for renal disease–the DIVINE study. Bone 2011;49:1317-22

96. Filleul O, Crompot E, Saussez S. Bisphosphonate-induced osteonecrosis of the jaw: a review of 2,400 patient cases. J Cancer Res Clin Oncol 2010;136:1117-24

97. Ravn P, Christensen JO, Baumann M, et al. Changes in biochemical markers and bone mass after withdrawal of ibandronate treatment: prediction of bone mass changes during treatment. Bone 1998;22:559-64

98. Idolazzi L, Fassio A, Gatti D, et al. Duration of treatment for osteoporosis. Reumatismo 2013;65:22-35

99. Ettinger B, San Martin J, Crans G, et al. Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. J Bone Miner Res 2004;19:745-51

Affiliation

Maurizio Rossini[†] MD PhD,
Giovanni Orsolini MD, Silvano Adami,
Vidya Kunnathully PhD & Davide Gatti MD
[†]Author for correspondence
University of Verona,
Department of Medicine,
Rheumatology Section,
Policlinico Borgo Roma,
Piazzale Scuro, 10; 37134,
Verona, Italy
Tel: +390456338607;
Fax: +390456338686;
E-mail: maurizio.rossini@univr.it