Pharmacokinetic profile of bisphosphonates in the treatment of metabolic bone disorders

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Summary

The pharmacokinetic profile of bisphosphonates is complex and depends on their potency in inhibiting bone resorption through their cellular effects and on the physicochemical action related to the interaction of these compounds with bone matrix. Amino-substituted bisphosphonates exert a more potent cellular effect on osteoclast via the inhibition of the mevalonate pathway, whereas non-nitrogen containing compounds exert a weaker effect deriving from the induction of intracellular metabolites in osteoclasts. For nitrogen-containing bisphosphonates there is a correlation between in vitro potency of inhibition of a specific enzyme, farnesyl pyrophosphate synthase, and their antiresorptive potency in vivo. Besides these effects on osteoclasts, bisphosphonates may in part mediate indirectly their antiresorptive activity through several effects on osteoblasts and osteocytes. Different binding affinities of bisphosphonates to hydroxapatite depend on both side chains structures and may explain how these drugs reach bone cells and exert their prolonged action in terms of adsorption and desorption processes. Clinical and animal models derived data indicate that agents with high anti-resorptive potency, favourable bone binding characteristics and good tolerability can be used with long between-dose intervals to optimize therapeutic outcomes.

KEY WORDS: bisphosphonates, metabolic bone disorders.

Introduction

A large body of evidences collected in the last decades indicates that bisphosphonates (BP) are the most potent and effective inhibitors of bone resorption in clinical use. These agents represent the treatment of choice for postmenopausal osteoporosis in which the BP class has consistently demonstrated good efficacy and tolerability in reducing fracture risk, in increasing bone mineral density and in reducing biochemical markers of bone turnover. In clinical practice BP use has been extended to all conditions characterised by excessive osteoclast-mediated bone resorption such as steroid-induced osteoporosis (1), Paget’s disease of bone (2) and tumour-associated osteolysis and hypercalcemia (3). Despite this widespread clinical use for more than three decades, our knowledge on pharmacokinetic and pharmacodynamic profile of BP is still incomplete mainly for the technical difficulties encountered in measuring their concentrations in biological fluids and for the difficulty in isolating large numbers of pure osteoclasts for performing biochemical and molecular studies. Differently from inorganic pyrophosphate, which is an endogenous regulator of bone mineralization with a P-O-P structure, BP contain two phosphate groups linked by phosphoether bonds to a geminal carbon atom (P-C-P structure) and this substitution makes BP extremely stable and resistant to biological degradation and therefore suitable for clinical use. The two covalently-bonded groups or side chains attached to the geminal carbon, usually referred as R1 and R2, allow a wide range of possible chemical structure. The available BP for clinical use share some pharmacological properties: they are poorly absorbed by intestine and are mainly captured by the skeleton where they bind strongly to hydroxapatite crystals, suppress osteoclast-mediated bone resorption and are retained for a long time within the skeleton. All BP are excreted unmetabolized in urine. In the traditional view the modification of the two side chains warrants different physicochemical, biologic, therapeutic and toxicologic characteristics of the different agents. According to this evidences the R1 chain represents the so called “bone hook” and the presence of a hydroxyl (OH) group at the R1 position gives the molecule the greatest affinity for bone (4, 5) whereas the molecular structure at the R2 position is responsible for the antiresorptive potency of the drug. According to the chemical structure at the R2 chain, BP can be subdivided into “non nitrogen-containing” BP (NN-BP) which have limited antiresorptive potency and “nitrogen-containing” BP (N-BP) which share an increased antiresorptive potency. Modification at the R2 chain of N-BP include lengthening the alkyl chain introducing a primary nitrogen (alendronate, pamidronate) and adding a tertiary nitrogen (ibandronate) or heterocyclic ring (risedronate, zoledronate). Since all N-BP have a hydroxyl group at the R1 chain, it should be argued that all the compounds in this class have the same binding affinity to bone mineral. This old view has been recently criticized, raising the question whether the R2 structure may contribute not only to the cellular but also to the physicochemical action of N-BP, strengthening the concept that the whole molecule is necessary to explain the complex action on bone and the differences observed among different N-BP. This short review is aimed to update the molecular mechanisms of action of BP and to review recent data about the bone binding characteristics and persistence in bone of the agents commonly used in clinical practice.

Molecular mechanisms of action of BP: cellular effects

Effects on osteoclasts

Structurally, BP have a three-dimensional shape and are capable of chelating divalent metal ions in a bidentate manner, by coordination of one oxygen from each phosphate group with the divalent cation (6). This binding is enhanced if one side...
chain is a hydroxyl or a primary amino-group, thus allowing a tridentate interaction (7). Owing to the high affinity of BP for di-valent ions, namely for Ca^{2+} ions, BP are rapidly cleared by the circulation and avidly bind to hydroxyapatite at site of exposed areas during active bone remodelling (8). Several evidences performed with radiolabelled BP have shown that at pharmacological doses these agents are able to concentrate at osteoclast-covered bone surfaces (8). This discovery, together with the fact that osteoclasts can internalise negatively-charged compounds by endocytosis (9), indicate that BP are capable to inhibit bone resorption via an intracellular effect on osteoclasts which leads to structural cellular changes, namely the loss of ruffled border (8). Other studies had demonstrated that BP are incorporated by calvarial cells in vitro (10) and that after in vivo administration BP can be visualized within endocytic vacuoles and other organelles in osteoclasts (8, 11). Furthermore, BP can be released from the bone surface in the acidic environment of the resorption lacuna beneath the osteoclast (8, 12). Taken together these observations indicate that osteoclasts are the cells in the skeleton that are most likely to be exposed to BP and that these agents inhibit bone resorption through an intracellular effect on osteoclasts. The mechanism of action of BP on osteoclastic cells has been widely studied and the proposed mechanisms include cytotoxic or metabolic injury of mature osteoclasts (13, 14), inhibition of osteoclast attachment to bone (15), inhibition of osteoclast differentiation or recruitment (16-20) or interference with osteoclastic structural features, namely the cytoskeleton, necessary for bone resorptive integrity (21-23). It has been proposed that although all BP act selectively on bone by virtue of their skeletal metabolism in osteoclasts. These compounds can be incorporated into non-hydrolysable, methylene-containing analogues of adenosine-triphosphate (ATP) reaching high concentrations in the osteoclast cytosol (25) and thus leading to the inhibition of various intracellular enzymes with detrimental effects on cell function and survival. The identity of these metabolites of the three main NN-BP, clodronate, etidronate and tiludronate, has been established by different techniques (26, 27), so that it can be assumed that the inhibition of bone resorption induced by NN-BP can be achieved by the unique mechanism of the incorporation of these agents into nucleotide analogues. As a result, this pathway causes caspase activation and apoptosis of osteoclasts probably via the inhibition of adenine nucleotide translocase, a component of the mitochondrial permeability transition process (28). Furthermore, recent data underscored that in etidronate-treated cells in vitro a caspase inhibitor, which is able to prevent apoptosis, maintained osteoclast number and most of the bone resorption and that this effect was maintained, to a lesser extent, when cells were treated with clodronate (29).

Differently from NN-BP, N-BP are not metabolised in vivo (26) thus suggesting an alternative mode of action. Available data indicate that this class of BP acts via the inhibition of farnesyl-pyrophosphate (FPP) synthase, an intracellular enzyme of the mevalonate pathway (6). A significant correlation has been reported between the order of potency for inhibiting human FPP synthase in vitro (either using partially purified or purified recombinant enzyme) (30, 31) (Table I) and the antiresorptive potency in vivo (31). Furthermore, minor modifications of the R2 side chain known to affect anti-resorptive potency in vitro were able to influence the ability to inhibit FPP synthase, thus definitely suggesting that this enzyme is the major pharmacologic target of N-BP in vivo (6).

The exact mechanism by which N-BP inhibit FPP synthase has received further attention but has not yet fully elucidated. The main hypothesis refers to the length and orientation of the R2 side chain which could affect the interaction of the nitrogen group with aminoacidic residues in the active site of the enzyme, thus explaining why minor changes at the R2 side chain influence the ability to inhibit FPP synthase (31, 32) markedly affecting anti-resorptive potency (4, 33-36). Independently on the molecular mechanism, the inhibition of FPP synthase blocks the cellular synthesis of isoprenoid lipids required for post-translational modification (prenylation) of small GTP-ase signalling geranylgeranylated proteins which are implicated in the regulation of a variety of cell functions leading to the arrangement of the cytoskeleton, membrane ruffling, trafficking of intracellular vesicles and apoptosis (37-40). The loss of prenylation of these GTP-ase signalling proteins induces another characteristic effect of N-BP, namely the loss of actin rings which represent a sort of adhesion structures, unique to osteoclasts, and that are essential in the attachment phase prior to the initiation of bone resorption (41). However, the loss of prenylation of small GTP-ases protein is probably a necessary but not sufficient event to explain N-BP-induced osteoclast apoptosis. In vitro studies indicate that the inhibition of bone resorption induced by alendronate and pamidronate was not associated with signs of toxicity or reduction of osteoclast number except at high concentrations (23, 42). Furthermore, it has recently been reported in an experimental model that the inhibition of apoptosis by a caspase inhibitor did not prevent inhibition of bone resorption with alendronate and risedronate and that the subsequent adjunct of geranyl geraniol, by restoring geranylgeranylation, returned bone resorption to control levels (29). These data indicate that N-BP suppression of bone resorption is strictly correlated to the enzymatic inhibition with apoptosis as a separate and possibly secondary event.

To support these observations on the mechanism of action of N-BP, data are available on the efficacy of statins which also inhibit the mevalonate pathway and prevent protein prenylation in inhibiting bone resorption by rabbit osteoclasts and in mouse calvarial cultures (43, 44), in preventing osteoclast formation in bone marrow cultures and in inducing apoptosis of mouse osteoclasts in vivo (43). Similarly to statins, N-BP have been shown to inhibit the incorporation of ^14C-mevalonate into both farnesylated and geranylgeranylated proteins in intact cells. The same effect has been demonstrated for N-BP in purified osteoclasts in vitro (30, 45) and in osteoclasts in vivo (46).

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>IC_{50} (nM), recombinant human enzyme</th>
<th>IC_{50} (nM), purified recombinant human enzyme</th>
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</thead>
<tbody>
<tr>
<td>Pamidronate</td>
<td>200</td>
<td>500</td>
</tr>
<tr>
<td>Alendronate</td>
<td>50</td>
<td>340</td>
</tr>
<tr>
<td>Incadronate</td>
<td>30</td>
<td>nd</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>20</td>
<td>nd</td>
</tr>
<tr>
<td>Risedronate</td>
<td>10</td>
<td>3.9</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>3</td>
<td>nd</td>
</tr>
<tr>
<td>Minodronate</td>
<td>3</td>
<td>nd</td>
</tr>
</tbody>
</table>

Table I - Values of IC_{50} for inhibition of human FPP synthase in vitro by nitrogen-containing bisphosphonates. Data are from Dunford et al. (31) using partially purified recombinant enzyme, or from Bergstrom et al. (30) using purified enzyme (nd = not determined). In both studies, clodronate and eldontrate had negligible effect on FPP synthase activity.
en together these observations provide definite evidence that the enzymatic inhibition of FPP synthase with consequent loss of protein prenylation in osteoclasts represent the major mechanism of action of this class of BP both in vitro and in vivo (6). As an alternative pathway on osteoclasts, several evidences have been collected on a direct inhibition by BP on different hydrolytic enzymes such as metalloproteases (47). This adjunctive mechanism may contribute to explain the overall inhibition of bone resorption since this process finally requires proteolytic degradation of bone matrix proteins. On the other hand, this mechanism may be at least in part responsible for the beneficial effect of BP in animal models of cartilage matrix damage in which cartilage degeneration was prevented when animals injected with chymopapain were pre-treated with zolendronic acid (48). Finally, BP can also inhibit protein tyrosine phosphatases which are essential for both osteoclast formation and osteoclastic resorptive activity (49), but the lack of correlation between this inhibition and the anti-resorptive potency leads to the potential conclusion that this is not the major mechanism by which these agents inhibit bone resorption in vivo (6).

The finding of the inhibition of osteoclast-like cells formation by BP in long-term cultures of human bone marrow (18) raised the question of a possible indirect inhibition of bone resorption by BP as a direct effect on mononuclear osteoclast precursors with prevention of osteoclast formation. To this respect, data have been published on a paradoxical increase in osteoclast number following BP administration as a possible consequence of a transient increase in PTH which in turn increases osteoclast recruitment (50). Later studies came to the conclusion that BP inhibit bone resorption without affecting osteoclast formation in vitro, suggesting that these agents act primarily on mature cells rather than on osteoclast precursors (42, 51, 52).

Effects on osteoblasts and osteocytes

Several reports have been focused on the effects of BP on osteoblasts and osteocytes indicating that these agents can stimulate the formation of osteoblasts precursors and of mineralized nodules in murine and human bone marrow cultures in vitro and can promote early osteoblastogenesis in mice in vivo (53). Moreover, etidronate promotes osteoblast differentiation in rat calvaria (54) and neridronate increases the proliferation of human osteoblastic cell in cultures (55). It has been shown in primary human trabecular cultures that both alendronate and risedronate increase osteoblast and osteoblast progenitor numbers (56). BP are believed to attenuate osteoblast and osteocyte apoptosis by activating extracellular signal-regulated kinases with anti-apoptotic activity (57). Further studies indicate that the prevention of osteocyte apoptosis is dose-dependent, is independent of the chemical structure of the BP, and is secondary to BP-induced opening of connexin 43 hemichannels at cellular level and that these effects are fully dissociable from the ability to inhibit FPP (58). Finally, in mice receiving glucocorticoids BP administration prevented glucocorticoid-induced osteoblast apoptosis (59). Since osteocyte and osteoblast viability might contribute to the maintenance of the mechanical competence of the skeleton, independently on bone mineral density (60), the effectiveness of BP in metabolic bone diseases may result, at least in part, from these actions on bone forming cells. However, since it is not known whether BP can directly affect osteoblastogenesis and osteocyte viability in vivo, the importance of these effects in humans remains to be fully elucidated.

Since the development of osteoclasts is controlled by osteoclastogenic factors synthesized by osteoblasts and bone marrow osteoblastic/stromal cells secrete the main components of the signalling pathway of the osteoprotegerin/RANK/RANK-ligand system, attention has been focused on the possible interactions between BP and the modulation of osteoclastogenesis driven by these mediators. Recent studies have shown that BP can decrease RANK-L mRNA expression in a rat osteoblast cell line (61) and increase osteoprotegerin mRNA and protein expression in human osteoblasts (62). These results were recently confirmed in a clinical study performed in a small group of postmenopausal women with osteoporosis in which alendronate and risedronate-treated patients had significantly increased serum levels of osteoprotegerin versus controls after 6 and 12 months of treatment which were positively correlated to changes in bone mineral density (63), whereas serum levels of RANK-L did not change throughout the treatment period. These data are in agreement with a previous in vitro study indicating that zoledronate may inhibit bone resorption by reducing transmembrane RANK-L expression and increasing osteoprotegerin secretion in osteoblastic-like cells leading to a decreased capacity of osteoblastic-like cells to support osteoclast formation (64). Taken together, these data strongly support the hypothesis that BP may indirectly mediate their antiresorptive activity through their action on osteoblasts.

Interactions with bone matrix

The clinical relevance of the cellular actions of BP derived from recent research data has limited the interest into their physicochemical properties. However, different skeletal binding properties among BP in healthy humans and in different clinical conditions can affect the pharmacokinetic of the individual compound thus influencing distribution to bone and long-term skeletal retention of these agents. This in turn can have clinical and therapeutic consequences in term of efficacy and persistence of action of the administered BP. Previous studies indicated that the presence of a OH group in R1 side chain increases the binding capacity to hydroxyapatite (HAP) and that this property was independent on the structure of the R2 side chain (4, 65). However, a recent in vitro study, employing a crystal growth method to assess the kinetic affinity constant of different BP, demonstrated the existence of significant differences in terms of affinity among hydroxyl-substituted BP, thus contributing to the hypothesis that the R2 chain is crucial not only for the cellular action but also for the physicochemical effect of the individual compound (66).

In theory, the amount of BP captured by the skeleton in vivo depends not only on its affinity for HAP but also on renal function and prevalent rate of bone turnover (67). In conditions of normal renal function and at a theoretical uniform level of bone turnover, informations about the amount of BP attached to the skeleton can be derived from urinary data. By subtracting the amount excreted in a 24-hour urine collection after intravenous administration, the whole body retention of the BP can be calculated. By this method, the retention of risedronic acid in healthy volunteers appears lower than that of other N-BP (alendronate and zoledronate), but the clinical significance of these findings has to be considered with caution since data were obtained in patients affected by different clinical conditions (68, 69). A partial support to the hypothesis of different binding affinity among N-BP comes from the only head to head report ever published using labelled risedronate and alendronate in humans at bio-equivalent doses. In this study after 72 hours a significant less amount of risedronate than alendronate had been retained, thus accounting for a different binding affinity of the two molecules (70). The clinical relevance of these observations is still debated, but is consistent with the observed effects on the more rapid rate of increase of biochemical markers of bone resorption after withdrawal in large clinical trials performed with risedronate as compared to alendronate (71, 72).
Furthermore, a recent head to head clinical trial showed that weekly alendronate determined a statistically significant 1.3 to 1.4-fold greater mean reduction of bone turnover markers than did weekly risedronate at common clinically used dosages (73). This difference would not be predicted by comparison of the effects on bone resorption of these N-BP in the rat in which risedronate is up to three-fold more potent. Again, these data are consistent with the reported significant difference of approximately 35% in kinetic binding affinities for HAP for risedronate and alendronate in a model of HAP crystal growth method (66). The dependency of bone attachment of BP on bone turnover has been extensively demonstrated by a study on labelled alendronate localisation in rat bone demonstrating that after administration the BP binds to exposed hydroxyapatite surfaces at sites prepared for undergoing bone resorption (8). Consequently, retention and subsequent release depend on available binding sites so that pharmacokinetics are likely to differ in various pathophysiological conditions. Furthermore, the amount of BP retained in the skeleton is also supposed to vary markedly between patients, particularly in diseases with relatively high interindividual variation in bone turnover such as Paget’s disease of bone where retention has been reported between 10 and 90% (74). In osteoporosis the variability is less, ranging for intravenous pamidronate between 47% and 74% (75). Data on BP retention in the same patients after repeated administration have not been published, but Cremers reports a personal observation of an intrapatient variation in skeletal retention of the administered BP not exceeding the 7% over a period of one year (67). Taken together, these observations suggest that the variability in skeletal retention across different clinical conditions and the interindividual variability play a crucial role in terms of biological effects and may account for differences in treatment response.

Differently from previous studies which by competitive binding approaches demonstrated only small differences (65, 76) or no significant differences (4, 77) in affinities among different N-BP, a recent study using a more sensitive HAP crystal growth method to determine the kinetic binding affinities of BP ranked the studied compounds according to their binding affinities as follows: zoledronate > alendronate > ibandronate > risedronate > etidronate > clodronate with a significant difference for the affinity constants (Table II) (66). This study took into account the effects of these BP also on other HAP surface properties potentially affecting the mineral binding of these agents in vivo such as zeta potential and interfacial tension. HAP zeta potential is the electrical potential at the crystal surfaces and it is influenced by local pH. Since it is suitable to change after the adsorption of highly charged anions such as BP (78-81), zeta potential may influence the subsequent binding of charged molecules. The observed changes in zeta potentials in the presence of different BP are likely to be related to the degree of protonation of the nitrogen moiety on the R2 side chain and this can account for the variable capacity of any given surface region of bone mineral to absorb different BP (66). Interfacial tension expresses the solid/liquid interfacial properties and plays an important role in the adsorption of molecules at solid/solution interfaces. It has been shown that HAP interfacial tension decreases with increasing BP binding and that the order of decreasing was similar to that of the affinity constants with the only difference of the interchanged position of etidronate and risedronate (66). Taken together these observations suggest that the differences among BP in terms of their effects on zeta potentials and interfacial tension may have relevance for BP interactions with the bone matrix (66) even if the clinical significance of these findings at present is still unclear (82).

Available data on relative binding affinities of BP for human bone may explain differences in the recovery of bone resorption after BP therapy has been stopped. Published data suggest that for etidronate given cyclically (83) and for daily risedronate (71) bone turnover returns to basal values within one year after withdrawal, whereas zoledronate induces a sustained inhibition of bone resorption for at least one year after a single intravenous dose of 4 mg (84). Oral alendronate given at 10 mg/day for 5 years shows an apparently long persistence with a suppression of bone resorption for up to 5 years after stopping (85). The variable persistence of the effects after withdrawal may reflect differences among BP in terms of their affinity for mineral binding but the clinical relevance of these data needs to be interpreted with some caution since this response can be influenced by the dose given and by differences in terms of basal turnover of the populations under study. Finally, and more importantly, no data have been published from head to head studies with different BP.

Studies on binding affinities of BP may provide important informations about how these drugs reach bone cells and exert their prolonged action in terms of adsorption and desorption process. To this respect, lower affinity BP exhibit a lower uptake, a higher desorption with a lower re-attachment and are embedded in bone in a more diffused fashion, whereas higher affinity BP are characterised by avid uptake, a lower rate of desorption with a higher re-attachment and a higher concentration in solution locally in the vicinity of bone cells (66). This model raises another intriguing question related to the activity and the fate of sequestred BP released by remodelling since it is not known whether and to what extent this amount of released compound will be pharmacologically active and furthermore able to suppress bone resorption. Several clinical studies performed with different BP indicated that withdrawal after prolonged periods of treatment was not associated with a rebound increase of bone turnover and rapid bone loss (71, 72, 86-89) as it was commonly seen after cessation of hormone replacement therapy (90). Taken together, these observations can support the hypothesis that amounts of the embedded BP which has been released from the skeleton are still pharmacologically active at bone surface but definitive data are lacking and no conclusions can be drawn about differences among individual agents (82).

Table II - HAP adsorption affinity constants of different bisphosphonates at pH 7.4.

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>$K_a/10^6$ L mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate</td>
<td>0.72 ± 0.12*</td>
</tr>
<tr>
<td>Etidronate</td>
<td>1.19 ± 0.10*</td>
</tr>
<tr>
<td>Risedronate</td>
<td>2.19 ± 0.17</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>2.36 ± 0.32</td>
</tr>
<tr>
<td>Alendronate</td>
<td>2.94 ± 0.24*</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>3.47 ± 0.18*</td>
</tr>
</tbody>
</table>

* Significantly different from risedronate $K_a$ (P<0.05) (from Nancollas et al. – ref. 66).

Conclusions

The pharmacokinetic profile of BP is complex and depends on their cellular effects and on the physicochemical action related to the interaction with bone matrix. To this respect, pharmacokinetic models must take into account several variables such as the potency of single agents in inhibiting bone resorption and the amount of BP bound to the skeleton and their long-term skeletal retention. Most clinical pharmacokinetic studies...
have used noncompartimental models but attempts are in progress to better define the pharmacokinetic of these agents by compartmental models taking into account the distribution of the drug not only in serum and bone surface but also in deep bone (75). Further pharmacokinetic/pharmacodynamic models have been developed taking into account a fourth compartment related to the time course of biochemical markers of bone resorption (91). These models have actual limitations since they have not been validated prospectively in different metabolic bone diseases and differences in binding and release of the individual agents from the skeleton, in oral bioavailability and in renal excretion make it necessary to calculate a separate pharmacokinetic profile for every individual BP (67).

From a clinical point of view, several studies published in recent years confirmed that a weekly administration of equipotent doses alendronate and risedronate can be as effective as daily dosing in maintaining bone mineral density and in reducing bone turnover over one or two years in large samples of postmenopausal women with osteoporosis (92, 93). According to this pharmacokinetic profile, the administration at increased drug-free intervals of high-dose BP requires agents with high anti-resorptive potency, favourable bone binding characteristics and good tolerability. This opportunity has been explored by recent studies reporting that in animal models the effects of ibandronate depends on the total dose irrespective of the drug-free interval (94). The importance of the total dose concept has been recently confirmed in a clinical study which for the first time reported that intermittently administered ibandronate given with a between-dose interval of more than 2 months has a prospectively demonstrated significant antifracture efficacy over 3 years in postmenopausal women with osteoporosis (95). Data presented at the ASBMR 28th Meeting on the effect of once-yearly infusion of zoledronic acid 5 mg on spine and hip fracture reduction in postmenopausal women with osteoporosis reinforce this hypothesis (96), thus demonstrating the viability of less frequent dosing of BP with potential benefits in terms of therapeutic outcome and patient adherence to treatment.

References

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