Alendronate and osteoporosis

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This is a review of the alendronate development program, starting with its pharmacological properties, current knowledge of its mode of action, preclinical studies of efficacy and bone safety. Then follows a brief review of the clinical studies, primarily the Phase III studies, which demonstrated increased bone density and provided preliminary data on fracture prevention, and the Fracture Intervention Trial studies, which demonstrated a reduction in the incidence of fractures of the spine, wrist, femur and all-site fractures. Alendronate and potentially other bisphosphonates can be useful drugs for the treatment and prevention of osteoporosis.

Osteoporosis is a reduction in bone mass and a change in bone micro-architecture that cause increased susceptibility to fractures. In most cases, including the highly prevalent postmenopausal osteoporosis, bone loss is a result of increased bone destruction (resorption) relative to bone formation. Both bone resorption and formation occur continuously in the skeleton as part of its normal function, during which packets of bone are being destroyed and rebuilt, a process called remodeling. Bone is resorbed by osteoclasts, which are multinucleated cells of hemopoietic origin whose number and activity increases in estrogen deficiency and in other conditions that can lead to bone loss, such as hyperparathyroidism, hyperthyroidism and glucocorticoid treatment. A rational strategy to treat and prevent osteoporosis is, therefore, inhibition of osteoclast activity. Bisphosphonates are the most effective inhibitors of osteoclastic bone resorption.

Geminal bisphosphonates are pyrophosphate analogs in which the oxygen in POP has been replaced by a carbon to yield the PCP backbone. Substitutions on the carbon yield a large family of compounds with different properties determined by the side chains. This review will focus on compounds that have been developed for bone therapy. In most of these compounds R_1 (Figure 1) is a hydroxyl group, which increases binding to the bone mineral (see below). The simplest R_2 is a methyl in etidronate, but it can be an aliphatic chain of different length with an amine in pamidronate, alendronate and neridronate, a branched chain in olpadronate and ibandronate, a ring compound in risedronate, incadronate, tiludronate and zoledronate (the list is not exhaustive). The potency of these compounds in inhibiting osteoclast activity differs by as much as 10,000-fold and is clearly influenced by the structure of R_2. This is illustrated by the increased potency of aminobisphosphonates relative to etidronate, by the higher activity of the four-carbon chain alendronate relative to the three-carbon chain pamidronate and the six-carbon chain neridronate, by the higher activity of the branched olpadronate compared with the linear pamidronate. This limited SAR suggests that R_2 fits into an 'active site' pocket as part of a specific molecular interaction or modifies the interaction of the rest of the molecule with the molecular target. However, the bisphosphonate group itself and R_1 must also be involved in the SAR determination since replacement of the hydroxyl group by an amine in olpadronate or pamidronate significantly reduced resorptive activity[1]. More detailed analysis of this SAR awaits identification of the molecular target(s).

General pharmacological properties of therapeutic bisphosphonates

The favorable pharmacological properties of these compounds are related to the bisphosphonate moiety. First and

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  1359-6446/98/$19.00. PII: S1359-6446(97)01134-3

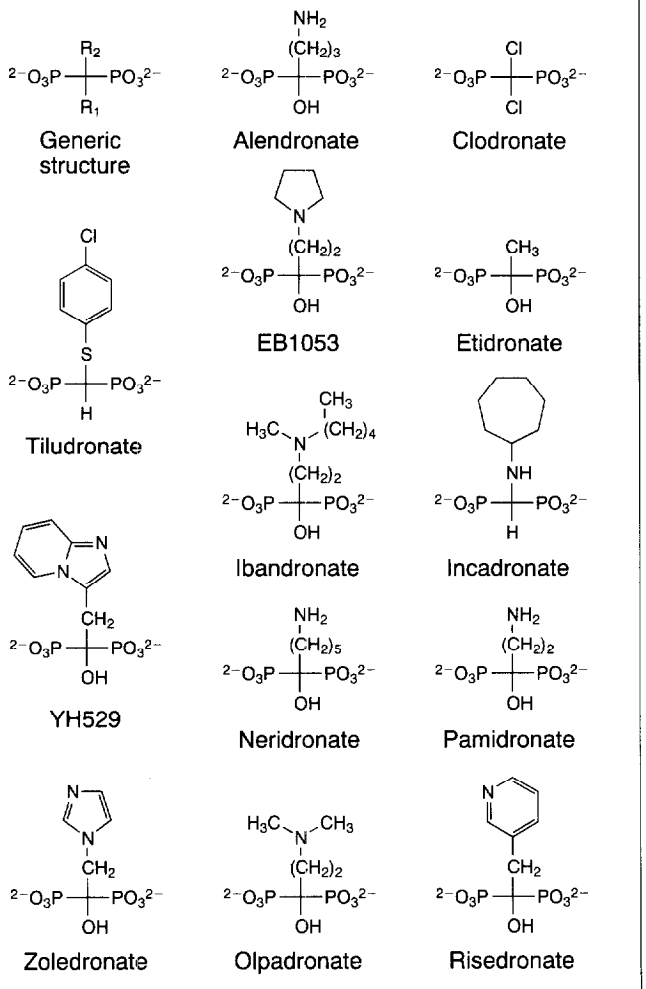

Figure 1. *Bisphosphonate structures*[42].

foremost, bisphosphonates bind to the bone mineral hydroxyapatite, possibly by single-pass removal from the circulation. The capacity of bone for bisphosphonates is extremely large. Equilibrium dialysis experiments with bone powder particles (180 mesh) show that saturation with alendronate would occur at millimolar concentrations[2], whereas the circulating concentration following a daily oral dose of alendronate is undetectable (i.e. <10 nM). This represents a gradient of 1 million to 1. Thus, although one cannot easily extrapolate from these *in vitro* experiments to the living skeleton, the data indicate that, although bisphosphonates are retained in the skeleton, it is virtually impossible to saturate it, especially with a potent bisphosphonate. Consistent with this conclusion, rats given a small initial intravenous dose of [^{3}H]alendronate, followed by a very high intravenous dose (35 mg kg^{-1} over 21 days, equivalent to 5 years of dosing for osteoporosis) and then again a small dose of [^{14}C]alendronate, showed equal uptake of the initial [^{3}H]alendronate and the posttreatment [^{14}C]alendronate dose, with no sign of saturation[3]. Skeletal uptake is one of the most desirable features of the bisphosphonates since it concentrates the drug in the target organ[2,4]. Bisphosphonates are virtually exclusively excreted by the kidney, in part by an active process. The combination of rapid clearance by the kidney and uptake in bone results in a relatively short circulating half-life and minimum exposure of nontarget tissues to the drugs[4]. Furthermore, the charge of the bisphosphonate group minimizes the cellular uptake of these compounds, which further reduces the drug exposure of nontarget tissues. On the other hand, the high polarity of the bisphosphonate group may be responsible for the low absorption of these compounds (1–5%, the more potent ones closer to the lower end of the range).

To summarize this section: the bisphosphonate moiety accounts for the unique properties of this class of compounds – concentration in the target tissue, rapid clearance in the kidney, limited exposure of nontarget tissues, and low absorption – which determine the pharmacokinetic profile and safety of these drugs.

Pharmacokinetics

The pharmacokinetics of alendronate have been studied in detail and were recently reviewed[4]. In animals and humans, absorption is about 0.7% and takes place primarily in the upper gastrointestinal tract. Absorption was found to be linear in the dosing range 5–80 mg. Following intravenous administration in rats, dogs, monkeys or pigs, approximately 50% is taken up by the skeleton and 50% is excreted in the urine; the same is true in humans. The fraction of skeletal uptake depends on the age of the animal, being higher in younger ones. Uptake in the skeleton is not homogeneous; it is highest at sites of active bone remodeling. The half-life in the circulation following intravenous administration in human subjects is approximately 1 h. In animals less than 1% of the injected dose can be retrieved from any tissue, other than bone, 48 h after administration. Absorption is relatively fast and the fate of the ingested alendronate parallels that of an intravenous tracer dose. As mentioned above, about 50% of the drug is retained in the skeleton when initially administered. This drug is released from the skeleton during skeletal remodeling. In rats, the terminal half-life is approximately 3 months, in dogs about 1 year, and in humans approximately 10 years. However, the half-life of bisphosphonate activity is much shorter, indicating that the bisphosphonate sequestered in bone is not pharmacologically active.

To summarize this section: bisphosphonate uptake is low (~1% for the more potent compounds), half the administered dose is taken up by bone and the balance is excreted in the urine, the half-life in the circulation is about 1 h, and the terminal elimination in humans is over 10 years.

Mode of action of bisphosphonates

The molecular mechanism for bisphosphonate inhibition of osteoclast activity has not been elucidated and it is not certain that all bisphosphonates act via the same mechanism. However, there is ample information on the mode of action of the bisphosphonates at the tissue and cellular level and several putative molecular targets have been identified[5].

At the tissue level, bisphosphonates reduce bone turnover by decreasing activation frequency, that is the number of sites at which bone remodeling is initiated. Thus, fewer packets of bone are being resorbed and reformed, which counters the effect of estrogen deficiency and other activators of bone resorption and results in bone preservation. The mechanism for this effect is inhibition of bone resorption, which occurs early in the remodeling cycle. The preservation of bone following estrogen deprivation has been documented for several bisphosphonates in rats and in nonhuman primates as well as in humans (see below) and is manifested in increased bone mineral content (BMC) or density (BMD), increased cancellous bone volume, thicker trabeculae, lower trabecular separation, a positive bone balance at the local level and, in cortical bone, reduced porosity. Treatment thus results in the maintenance of both the amount of bone and bone structure.

At the cellular level, bisphosphonates clearly suppress osteoclastic bone resorption. There is *in vitro* or *in vivo* evidence for three ways by which this effect might be produced: (1) decreased osteoclast formation, (2) decreased osteoclast activity, and (3) reduction of osteoclast lifespan (reviewed in Ref. 5).

Decreased osteoclast formation produced by bisphosphonates has been observed in culture and attributed to action on osteoblasts, which support osteoclast formation. Short exposure of osteoblastic cells to potent bisphosphonates leads to the production of a diffusible osteoclast inhibitory activity with a molecular mass of less than 10 kDa. *In vivo*, the number of osteoclasts initially increases after pamidronate or alendronate administration; however, the number of osteoclasts decreases with prolonged treatment. The quantitative contribution of this effect to the suppression of osteoclast activity *in vivo* remains to be established.

Direct inhibition of osteoclast activity was proposed many years ago to result from osteoclast ingestion of the bisphosphonate. Recent evidence for alendronate shows preferential localization on bone resorption surfaces within 4 h after administration, the presence of alendronate inside osteoclasts in tissue sections 12 h after administration, and the subsequent disappearance of the osteoclast convoluted membrane, consistent with osteoclast inactivation. A physiological manifestation of lack of convoluted membrane (ruffled border) is the inability of osteoclasts seeded on alendronate-treated bone to extrude protons (acidify) (see Ref. 5). This mode of action of bisphosphonates seems to require cellular uptake of the drug, which was also reported to be the case for tiludronate interference with the formation of actin rings in osteoclasts[6] and with the effect of bisphosphonates on *Dictyostelium discoideum*, where uptake by pinocytosis seems to be required[7].

The third proposed mechanism is a reduction in osteoclast lifespan resulting from apoptosis, shown to be induced by risedronate both *in vitro* and *in vivo*[8]. It is not clear if this is a primary effect reflecting direct activation of an apoptotic pathway or if it is secondary to osteoclast inactivation and detachment. As mentioned above, these three pathways are not mutually exclusive and the contribution from each of them to inhibition of osteoclast activity *in vivo* by the various bisphosphonates remains to be established.

The molecular targets of bisphosphonates are still under investigation. SAR strongly suggests specific molecular interactions rather than nonspecific toxic effects. The inhibition of osteoclast formation by exposure of osteoblastic cells for a short time to low bisphosphonate concentrations suggests there are cell-surface receptors for bisphosphonates. However, none have been found so far and no second messengers have been detected. Several enzymes that could be involved in the regulation of osteoclast activity were shown to be inhibited by bisphosphonates. Squalene synthase and other enzymes involved in cholesterol metabolism are inhibited by bisphosphonates, possibly because of the role of farnesyl pyrophosphate in this pathway. Interestingly, mevastatin mimics the effect of alendronate on osteoclast formation and the action of both was inhibited by mevalonic acid[9]. Several protein tyrosine phosphatases (PTPs) are inhibited by bisphosphonates, and inhibitors of PTPs, such as vanadate and phenyl arsine oxide, inhibit osteoclast formation and bone resorption[10].

Safety and efficacy of bisphosphonates in preclinical studies

Guidelines of several regulatory agencies for the registration of drugs for the treatment and prevention of osteoporosis

stipulate demonstration of efficacy and safety, including specifically bone safety in animal models of osteoporosis. For example, the FDA Draft Guidelines recommend that, for postmenopausal osteoporosis: (1) drugs should be evaluated in two species (ovariectomized rats and larger animals, such as nonhuman primates) for a duration of 1–2 years; (2) evaluation of efficacy should be based on parameters similar to those used in the clinic, such as BMD and biochemical parameters of bone turnover; and (3) evaluation of safety should include, in addition to the usual toxicology studies (cytotoxicity, carcinogenicity, genotoxic and organ histopathology studies), specific bone safety studies based on histomorphometry and biomechanical evaluation. Data on the first drug that followed this development program, alendronate, will be used here for illustration, but similar findings were obtained with other bisphosphonates, such as risedronate, tiludronate, ibandronate and incadronate.

In the commonly used model of estrogen deficiency osteoporosis, the ovariectomized rat, all bisphosphonates tested were shown to prevent bone loss when given soon after ovariectomy and to arrest or reverse bone loss when given to osteopenic animals, beginning several months after ovariectomy. For example, in an alendronate study rats were ovariectomized at 3 months, treatment was started 4 months later and was continued for 6 months with doses ranging between 0.28 and 28 μg kg^{-1} s.c. twice weekly. At the end of the experiment, the biomechanical properties of vertebrae and femora were evaluated. Neither in the ovariectomized animals nor in the treatment animals was there a difference in the strength of the shaft of the femora, which is due in part to increased periosteal growth in estrogen deficiency and to the mechanical adaptation of the rat long bones, which increase their diameter (moment of inertia) to increase strength. In the cancellous bone, however, both in the subepiphyseal region of the tibia and in the vertebrae, there was a significant loss. Mechanical testing of the vertebrae showed a 30% reduction in bone strength (ultimate load) in ovariectomized animals, compared with nonovariectomized controls. Alendronate administration at 2.8 and 28 μg kg^{-1} maintained bone strength at control levels[11]. Furthermore, when bone strength (ultimate load) was correlated with bone volume in the L6 vertebra, the predicted curvilinear correlation between strength and mass was observed (Figure 2), indicating that the quality of the bone was normal. Similar results have since been reported for other bisphosphonates.

The fact that this method can detect changes in bone quality was shown in minipigs treated with fluoride[12]. Nine-month-old minipigs were treated with either sodium fluoride (2 mg kg^{-1} $days^{-1}$ p.o.) or alendronate (1 mg kg^{-1} $days^{-1}$ p.o.) or vehicle for 1 year. In alendronate-treated animals, bone strength in the L4 vertebra showed the expected positive correlation with bone volume ($P < 0.02$). However, in sodium-fluoride-treated animals, bone strength did not increase with bone volume. Moreover, when bone strength was plotted against fluoride content, there was a significant negative correlation, i.e. decreased strength with increased fluoride. Further analysis of the mineral in these bones showed changes in the dimensions of the hydroxyapatite crystals and their small-angle X-ray scattering pattern, which correlated with the change in bone strength[13]. These findings indicate that, for alendronate and probably other potent bisphosphonates, the structure of the bone is not altered by treatment. On the contrary, the reduction in turnover may actually improve bone quality and decrease susceptibility to fractures. These conclusions were supported by studies in nonhuman primates.

The first bisphosphonate studies were also conducted with alendronate in ovariectomized baboons[14]. In this prevention study, baboons received alendronate every 2 weeks (0.05 or 0.25 mg kg^{-1} i.v.). The ovariectomized baboons lost

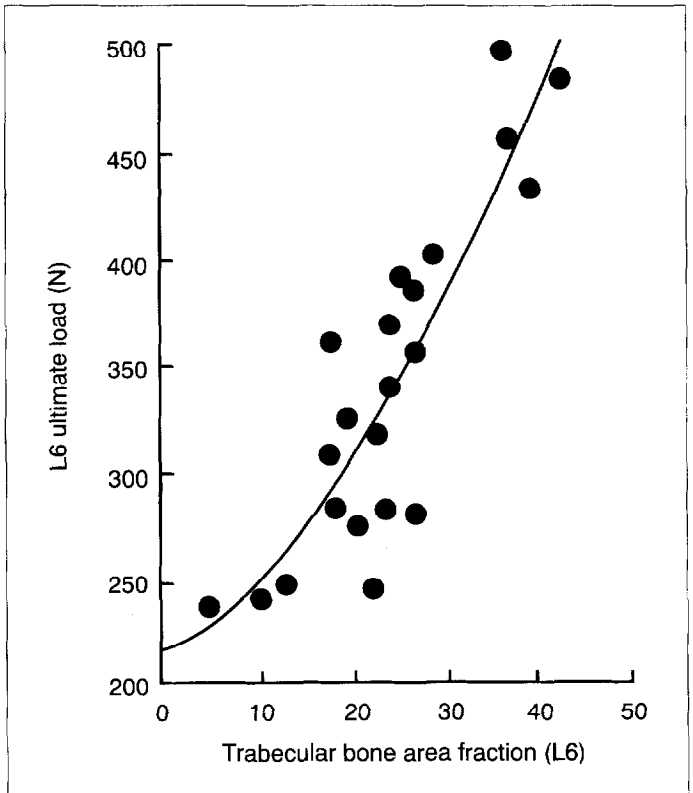

Figure 2. *Bone mass versus bone strength ($r^2 = 0.77$, n = 22).*

bone in the spine (documented by bone density measurement and histomorphometry) as well as in the iliac crest. The bone loss was prevented (by the low dose) or reversed (by the higher dose) by alendronate, which produced an increase above controls. As in the other studies described above, there was a positive correlation between the mechanical strength of the vertebral trabecular bone and the bone mass, vertebrae from animals treated with the higher dose of alendronate showing the highest volume and strength, while ovariectomized animals treated with vehicle showed the lowest strength.

In view of the accumulation of bisphosphonates in the skeleton, special preclinical bone safety studies are advised: for example, long-term treatment with a multiple of the therapeutic dose, since etidronate and clodronate at high doses caused spontaneous fractures in dogs treated for 1 year[15]. No fractures were observed in dogs treated with five times the therapeutic dose of alendronate for 3 years[16]. Moreover, experimental fractures in dogs (osteotomy) showed healing comparable to that of controls with no decrease in callus strength 16 weeks after osteotomy[17].

To summarize this section: treatment of rats or larger animals, such as nonhuman primates, immediately after ovariectomy, or following bone loss, with alendronate or other recently developed potent bisphosphonates prevents or reverses bone loss and maintains normal bone quality as assessed by both histological and biomechanical analysis.

Clinical use of bisphosphonates in the treatment of osteoporosis

The findings described above are the basis for taking these compounds into clinical trials. Alendronate was the first of the newer bisphosphonates to be developed for the treatment and prevention of osteoporosis.

This section summarizes current data on the efficacy and safety of bisphosphonates in humans in the treatment of osteoporosis. Very recently, data have become available to indicate that bisphosphonates may also have value in preventing osteoporosis, and alendronate has become available in the USA for that indication. However, this review will focus on the treatment of women who already have osteoporosis since most of the published literature pertains to this population.

Osteoporosis is a systemic skeletal disease in which low bone mass and reduced bone strength lead to increased risk of fracture[18]. Approximately 40–50% of 50-year-old white women will sustain one or more osteoporosis-related fractures over their remaining lifetime[19,20]. Excess mortality during the year following hip fracture has been estimated at 10–20%, and up to 33% of patients with hip fracture require long-term nursing-home care[20]. Vertebral fractures are also an important outcome of osteoporosis since they can lead to chronic back pain, loss of height, and restricted mobility. In the future, the situation will clearly worsen as a result of the continuing aging of the population[19]. Several prospective epidemiological studies confirm a strong and consistent relationship between low bone mass and increased risk of fracture[21,22].

Osteoporosis treatments aim to prevent or reverse bone loss at clinically important sites to reduce the risk of fractures in patients with low bone mass. Several therapies other than the bisphosphonates, such as estrogen, calcitonin, fluoride salts and ipriflavone, are available in certain countries for the treatment of osteoporosis. Of these, only estrogen has clear efficacy to increase bone mass at the spine and hip and to reduce the incidence of fractures[23–25]. However, limited tolerability, increased risk of endometrial cancer (with unopposed estrogens) and the fear of an increased risk of breast cancer limit the acceptability of estrogen treatment for many postmenopausal patients with osteoporosis[24].

As is the case for preclinical studies, the greatest amount of clinical data exists for alendronate, and this review will therefore focus on the use of this agent. Differences between bisphosphonates in potency and possibly also in the precise mechanism of action may be important in defining their efficacy and safety in the treatment and prevention of osteoporosis. For example, etidronate impairs mineralization at doses used clinically, and may give rise to osteomalacia[26,27], whereas the newer, more potent bisphosphonates do not. Thus, although bisphosphonates share many common features, each needs to be considered separately with respect to their clinical features.

Early clinical studies of bisphosphonates in osteoporosis

The earliest studies of bisphosphonates in the treatment of osteoporosis involved continuous daily administration of etidronate. The rate of bone turnover decreased, but treatment was also associated with histological evidence of osteomalacia[28,29]. These early negative results deterred further clinical study of the use of bisphosphonates in osteoporosis. Subsequently, Frost[30] postulated that a cyclical regimen with administration of a stimulator of bone resorption immediately followed by use of an osteoclast inhibitor, such as a bisphosphonate, might induce positive bone balance. Since it was believed that cyclical administration of etidronate would allow remineralization of bone in the off-drug phase,

this reawakened interest in the use of this agent. Three studies were performed: one in Denmark[31] and two in the USA. The latter two studies, combined for presentation[32,33], demonstrated significant increases in spine BMD with small effects also seen at the hip. Although both studies showed a trend towards fracture risk reduction, neither study showed a significant effect in reducing fracture risk over 3 years when the entire study population was included in the analysis[31,32]. Thus, although it seems likely that the increases in bone mass seen with etidronate should provide some reduction in fracture risk, this remains to be demonstrated in a randomized clinical trial.

Until quite recently it had been believed that antiresorptive agents could only increase bone mass over a finite period of about 6–12 months, and that bone loss would resume beyond that time. However, this dogma came into question as a result of a report from Valkema and coworkers[34]. Their small, open-label study showed that continuous daily administration of an aminobisphosphonate, pamidronate, was associated with a progressive increase in bone mass over 4 years. However, further work with oral pamidronate was not pursued, since the doses used were associated with significant upper gastrointestinal irritation. Nonetheless, this study demonstrated the potential of bisphosphonates in the treatment of osteoporosis and stimulated further research with other bisphosphonates, such as alendronate, risedronate and tiludronate. To date, substantive data are available only for alendronate; the other compounds remain under investigation.

Effects of alendronate on bone turnover

As anticipated, alendronate decreased the rate of bone turnover, as judged by decreases in urinary deoxypyridinoline excretion and serum osteocalcin, which are highly specific markers of resorption and formation, respectively. Alendronate reduced deoxypyridinoline to a new steady-state level approximately 50% below baseline after 1–3 months of treatment; this was followed by a plateau, which was maintained during the remainder of the treatment period[35]. Later decreases in osteocalcin and bone-specific alkaline phosphatase, which reached a plateau after 6 months of treatment, reflect the anticipated indirect effect of alendronate to decrease bone formation through a reduction in the number of active bone remodeling sites[35]. Importantly, no further decreases in the specific biochemical markers of bone turnover were observed after the first 6 months, indicating that alendronate does not have a cumulative effect on suppressing bone turnover despite continued administration[36]. The on-treatment values for each of the biochemical markers were indistinguishable from those seen in healthy premenopausal women, suggesting that, at the total skeletal level, the rate of turnover had been reduced to values comparable to those in normal estrogen-replete women[35].

Effects of alendronate on BMD

The efficacy of alendronate in increasing BMD (or BMC) was comparable in each of the studies. BMC or BMD (BMC corrected for cross-sectional area) measures the attenuation of an X-ray beam across the bone and is determined by the amount of bone (bone mass) and its mineral content. Despite calcium supplementation, significant decreases in BMD of the spine, femoral neck, trochanter and total body relative to baseline, in the range of 0.7–1.2%, occurred in the placebo group (pooled across the Primary Phase III Studies) over 3 years[37]. In marked contrast, alendronate induced highly significant and clinically meaningful increases in

Table 1. Mean percentage change[a] in bone mineral density at month 36 relative to placebo in Phase III studies[37]

Daily treatment	Spine	Femoral neck	Trochanter	Total body
Alendronate 5 mg				
US Primary Phase III	6.3 (0.5)	4.5 (0.7)	6.0 (0.7)	1.2 (0.4)[b]
Multinational Primary Phase III	5.4 (0.7)	3.5 (0.7)	5.1 (0.9)	1.9 (0.3)
Combined	5.9 (0.4)	4.0 (0.5)	5.6 (0.6)	1.6 (0.3)
Alendronate 10 mg				
US Primary Phase III	10.3 (0.5)	6.3 (0.7)	8.3 (0.7)	2.5 (0.4)
Multinational Primary Phase III	7.4 (0.7)	5.5 (0.7)	7.2 (0.9)	2.6 (0.3)
Combined	8.8 (0.4)	5.9 (0.5)	7.8 (0.6)	2.5 (0.3)
Alendronate 20/5 mg				
US Primary Phase III	8.6 (0.5)	4.8 (0.7)	8.0 (0.7)	2.8 (0.4)
Multinational Primary Phase III	8.4 (0.7)	4.2 (0.7)	7.2 (0.9)	2.6 (0.3)
Combined	8.5 (0.4)	4.5 (0.5)	7.6 (0.6)	2.7 (0.3)

[a]SE given in parenthesis.
[b]Significantly different from placebo $P \leq 0.01$; all other values $P \leq 0.001$.

BMD at each of these skeletal sites. As can be seen from Table 1, comparable increases in BMD relative to placebo at each measurement site were observed in the 10 mg and 20/5 mg groups, despite a total cumulative dose that was 50% higher in the latter group. Significantly smaller effects were observed with 5 mg at each measurement site.

Over 96% of patients in these two studies treated with alendronate 10 mg had an increase in spine BMD relative to baseline. The observed smaller increase in total body BMD was anticipated since most of the skeleton consists of cortical bone, which turns over much more slowly than trabecular bone. The increases in total body and forearm BMD are important, because they indicate that the gains in bone mass seen at the spine and hip did not occur at the expense of bone elsewhere in the skeleton.

As shown in Figure 3, the 10 mg dose was associated with more rapid increases than 5 mg throughout the period of study and, interestingly, the gains in bone mass at the spine and hip during the third year were greater in the 10 mg group than in the group that had received alendronate 20 mg for 2 years before being switched to 5 mg in the third year. These findings support the selection of 10 mg as the dose for treatment of osteoporosis.

The increases were most rapid during the initial 6–12 months, but continued throughout 3 years of treatment with alendronate. Moreover, the increases observed in the group treated with alendronate 10 mg were approximately linear between month 12 and month 36 at each of the four measurement sites. The early rapid increase in bone mass is clearly explained, at least in part, by the reduction in remodeling space that is known to occur when the rate of bone turnover is reduced. However, the mechanism for the continued progressive increases over the 3 years of treatment is less certain. Such an effect might be related to a positive bone balance at the bone structural unit (BSU) level caused either by a reduction in resorption depth and/or by an increase in the width of new bone formed at each remodeling site, possibly in response to the observed increase in parathyroid hormone. In addition, an increase in the degree of mineralization resulting from maturation of BSUs could account for some continued increase in bone mass.

The sustained efficacy of alendronate is dependent on continued administration. In the Phase IIb study, there were greater increases in spine and hip BMD in patients who received 10 mg continuously for 2 years than in patients who received the same total dose as 20 mg for 1 year, followed by placebo in year 2 (Ref. 36). Reduction of bone turnover also became attenuated following discontinuation of alendronate in that study[36], further confirming that efficacy is primarily dependent on continued administration of drug rather than cumulative exposure.

Effects of alendronate on bone quality

Transiliac bone biopsies were obtained at either 2 or 3 years from 231 patients (133 on alendronate) from the two

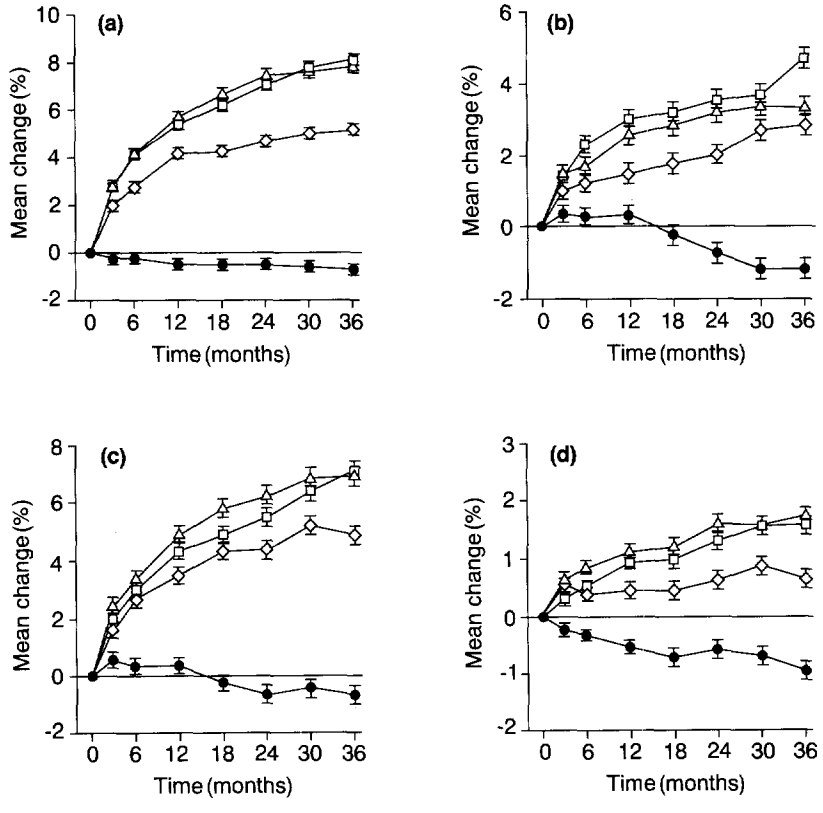

Figure 3. *Effect of alendronate on bone mineral density in the combined Primary Phase III Studies[37]: percentage change from baseline (mean ± SE). Symbols are as follows: open diamonds, squares and triangles show the 5 mg, 10 mg and 20/5 mg dosing groups, respectively; closed cirles show placebo.*

Primary Phase III Studies, and a further 187 biopsies (137 on alendronate) were obtained at either 1 or 2 years from patients in the Elderly Study. Results from these studies confirm that alendronate has no adverse effects on either bone mineralization or microstructure at doses of up to 20 mg kg^{-1} for up to 3 years (up to 2 years at the 20 mg dose)[38,39]. Analysis of three parameters of skeletal mineralization – osteoid thickness, osteoid volume, and mineral apposition rate – confirmed that mineralization proceeds normally in osteoporotic women, even following continuous daily treatment with alendronate for 3 years in the highest dose group (20/5 mg). As expected from its mechanism of action, alendronate decreased, but did not completely suppress, the rate of bone turnover as assessed by a decrease in the mineralizing surface. Also, based on histomorphometric identification of bone-forming activity, there was no evidence that bone turnover was suppressed completely. In all biopsies, normal lamellar bone was seen without any evidence of osteomalacia, woven bone, marrow fibrosis or cellular toxicity as a result of treatment with alendronate. Thus, the data clearly demonstrate that bone formed during treatment with alendronate is of normal quality.

Table 2. Incidence and relative risk (RR) of incident vertebral fractures in the Vertebral Fracture Arm of the Fracture Intervention Trial[40]

Event	Treatment assignment		Alendronate versus placebo	
	Placebo (n = 965)	Alendronate (n = 981)	RR with 95% CI	P
Patients with one or more fractures[a]	145 (15.0%)	78 (8.0%)	0.53 (0.41–0.68)	<0.001
Patients with two or more fractures	47 (4.9%)	5 (0.5%)	0.10 (0.04–0.22)	<0.001
Patients with a painful vertebral fracture	50 (5.0%)	23 (2.3%)	0.45 (0.27–0.72)	<0.001

[a]P = 0.256 for consistency of treatment effect across centers.

Effects of alendronate on fracture incidence

Data on the antifracture efficacy of alendronate are derived from the Vertebral Fracture Arm of the Fracture Intervention Trial (FIT)[40], the Phase III studies[37] and the premarketing studies as a whole[41].

The incidence and relative risk of sustaining at least one vertebral fracture (primary endpoint), two or more such fractures, or a painful (clinically apparent) vertebral fracture in patients in the Vertebral Fracture Arm of the FIT are shown in Table 2. Very similar decreases in the risk of vertebral fractures were obtained in the alendronate Primary Phase III Studies (Figure 4).

Therefore, the Vertebral Fracture Arm of FIT both confirmed the vertebral antifracture efficacy of treatment seen in Phase III and gave greater confidence with regard to the magnitude of the fracture risk reduction that can be anticipated from treatment with alendronate; it also showed that this reduction is of direct clinical relevance, with an important decrease in the number of symptomatic events.

Clinical fractures

In the Vertebral Fracture Arm of the FIT, the time to occurrence of the first clinical (symptomatic vertebral or nonvertebral) fracture was evaluated using life-table analysis. A total of 183 (18.3%) of the 1,005 patients who received placebo experienced at least one clinical fracture as opposed to 139 (13.6%) of the 1,022 patients randomized to alendronate. The respective fracture rates were 6.99 and 5.06 clinical fractures per 100 patient years at risk (PYR), and there was a 28% risk reduction (RR 0.72; 95% CI 0.58–0.90) in the alendronate group compared with placebo (P = 0.004). The life-table survival curve is shown in Figure 5.

These data are similar to the 29% reduction in nonvertebral clinical fractures observed in the meta-analysis of the

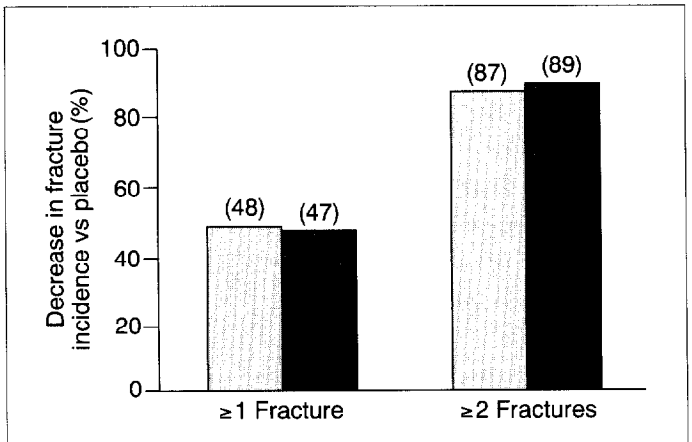

Figure 4. *Comparison of the percentage reduction in vertebral fracture incidence in the Primary Phase III Osteoporosis Studies[37] (pale bar) and the Fracture Intervention Trial[40] (dark bar).*

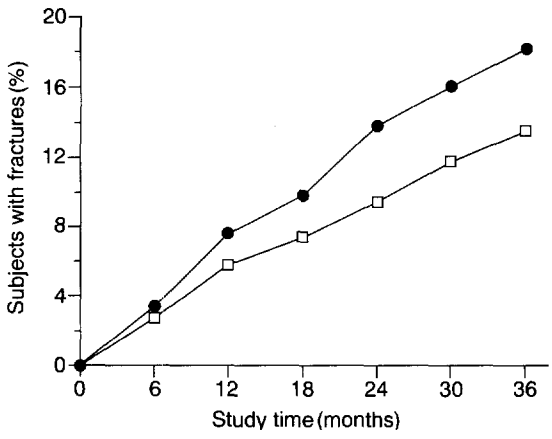

Figure 5. *Cumulative incidence of patients with any clinical fracture in the Fracture Intervention Trial. Symbols are as follows: closed cirlces, placebo; open squares, alendronate.*

five premarketing alendronate studies excluding FIT (RR 0.71; 95% CI 0.502–0.997; $P \approx 0.48$)[41].

Hip fractures

The incidence of hip fracture was evaluated in the same way as all clinical fractures. In FIT, a total of 22 (2.2%) of the 1,005 patients who received placebo experienced a hip fracture, whereas only 11 (1.1%) of the 1,022 patients randomized to alendronate did so. The respective fracture rates were 0.77 and 0.37 clinical fractures per 100 PYR, with a 51% risk reduction (RR 0.49; 95% CI 0.23–0.99) in the alendronate group compared with placebo (P = 0.047). Similarly, the meta-analysis of the five premarketing studies showed that alendronate decreased the incidence of hip fracture by 54% relative to placebo (P = 0.15), which is comparable with the 51% decrease observed in FIT (Refs 40,41).

These data are critically important, because this is the first time for any treatment intervention that a prospective randomized controlled clinical trial has demonstrated efficacy in reducing the incidence of hip fractures in a free-living population of women. Since hip fractures are associated with the greatest suffering and cost resulting from osteoporosis, this finding of an approximate halving in the incidence of hip fracture has clearly indicated the important benefits to patients that can be expected from treatment with alendronate.

Forearm fractures

In the Vertebral Fracture Arm of FIT, a total of 41 (4.1%) of placebo-treated patients compared with 22 (2.2%) of those randomized to alendronate experienced a forearm fracture. The respective fracture rates were 1.44 and 0.75 forearm fractures per 100 PYR (Ref. 40). Thus, the incidence of forearm fracture was reduced by 48% in the alendronate group compared with the placebo group (P = 0.013). As with hip fracture, the incidence of forearm fracture over time in the alendronate groups was lower than in the placebo groups in both study populations. At study end, the incidence of forearm fracture in the meta-analysis of the five premarketing studies was decreased by 61% (P = 0.006), which somewhat exceeded the 44% decrease in forearm fractures observed in FIT (Ref. 41).

Clinical safety of alendronate

In the Primary Phase III Studies, the FIT and other osteoporosis studies, the overall safety profile of alendronate 5–20 mg is remarkably similar to that of placebo. As shown in Table 3, comparable proportions of patients with various categories of adverse experiences (AEs) were observed in the Primary Phase III Studies across all treatment groups, including withdrawals because of AEs, a good indicator of the overall tolerability of a pharmaceutical therapy.

The safety experience with doses of alendronate up to 20 mg in the other studies is entirely consistent with that observed in the Primary Phase III Studies. All bisphosphonates are

Table 3. Summary of safety data from the Primary Phase III Studies[37]

Adverse experiences (AEs)	Placebo	Alendronate 5 mg	Alendronate 10 mg	Alendronate 20/5 mg
Total number enrolled	397	202	196	199
Any clinical AE	358 (90.2%)	181 (89.6%)	173 (88.3%)	177 (88.9%)
Drug-related AE[a]	101 (25.4%)	56 (27.7%)	53 (27.0%)	62 (31.2%)
Serious clinical AE[b]	69 (17.4%)	26 (12.9%)	27 (13.8%)	32 (16.1%)
Withdrawn due to AE	24 (6.0%)	11 (5.4%)	8 (4.1%)	16 (8.0%)
Death	3 (0.8%)	1 (0.5%)	2 (1.0%)	0
Any laboratory AE	127 (32.1%)	66 (33.0%)	66 (34.6%)	57 (28.8%)
Drug-related laboratory AE[a]	37 (9.3%)	27 (13.5%)	12 (6.3%)	16 (8.1%)
Withdrawn due to laboratory AE	1 (0.3%)	2 (1.0%)	0	0

[a]Considered possibly, probably or definitely related to study drug by the investigator.
[b]A serious AE is one that results in hospitalization, is life-threatening, causes permanent disability or is a cancer (and is not necessarily related to the study drug).

known to be able to induce upper gastrointestinal local irritation. However, the incidence of upper gastrointestinal AEs was similar among groups on placebo and alendronate for doses up to 20 mg. When upper gastrointestinal AEs occurred, they did not lead to discontinuation of alendronate 10 mg any more frequently than of placebo (1% and 2%, respectively). Of all upper gastrointestinal AEs, abdominal pain and dysphagia were the only AEs that occurred significantly more often in patients treated with alendronate 10 mg than in those treated with placebo. The abdominal pain events occurred most often within the first few months after treatment initiation and rarely led to patient withdrawal. In early postmarketed use, some cases of esophagitis and/or esophageal ulcer were reported[40]. These events occurred particularly in patients who did not follow the dosing instructions and probably relate to the irritant potential of refluxed gastric acid containing alendronate. The rate of such reports has since declined despite the much more widespread use of alendronate, suggesting increased awareness and compliance with dosing instructions (for example, patients should take alendronate before breakfast with at least 6 ounces of water and not lie down until after their first food of the day). Recent preclinical safety studies in dogs suggest that the effects on the esophagus are caused by reflux and are not unique to alendronate, because risedronate and tiludronate also induce esophageal lesions under similar conditions (C.P. Peter, unpublished). Discontinuation, recommended in patients who do not tolerate the drug, has prevented serious adverse effects.

Conclusions

Bisphosphonates are specific inhibitors of osteoclastic bone resorption that have found broad applicability in the treatment of disorders such as Paget's disease and hypercalcemia of malignancy, disorders that are characterized by excess bone resorption. Recently, the utility of bisphosphonates in the treatment and prevention of osteoporosis has become the topic of very active research. Of the older bisphosphonates, etidronate has become available in some countries for the treatment of osteoporosis; however, it produces relatively modest increases in BMD, especially at the hip. Definitive fracture data are still awaited for etidronate and there remain some concerns because of the known potential of this agent to induce osteomalacia. In contrast, alendronate has been clearly demonstrated to increase bone mass at the spine, hip and total body and to reduce the incidence of both vertebral and nonvertebral fractures, including those of the hip and forearm. The normal quality of bone formed during treatment with alendronate has also been clearly demonstrated in both preclinical and clinical studies. The clinical studies also indicate that alendronate at dosages of 5 and 10 mg is generally very well tolerated and has an excellent safety profile. The results from the Phase III studies of tiludronate and risedronate are not yet available, and it remains to be seen whether these and other bisphosphonates can achieve similar effects on bone mass and fracture risk to those documented for alendronate and whether the anti-osteoporotic efficacy extends to other members of this class.

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