



Bisphosphonates

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Bisphosphonate therapy has become the preferred treatment option to reduce the risk of spine and hip fractures in men and women with involution and glucocorticoid-induced osteoporosis. By suppressing bone turnover, bisphosphonates prevent bone loss and preserve bone architecture. Fracture reduction has been demonstrated in patients who are at high fracture risk. When administered appropriately, these drugs are well tolerated and have an excellent safety profile. The challenges to clinicians are to identify the patients for whom bisphosphonate therapy is indicated and to devise dosing and monitoring strategies to enhance the long-term adherence to therapy required to realize the full benefits of these treatments.

Bisphosphonates are synthetic stable analogs of pyrophosphate with potent effects on skeletal metabolism [1]. The primary effect of the agents is to suppress osteoclast-mediated bone resorption, and indirectly they decrease osteoblast activity [2]. They should be considered anti-remodeling drugs and differ from bone-forming anabolic agents. These effects have been exploited for the treatment of various metabolic bone disorders including several forms of osteoporosis, Paget's disease, hypercalcemia of malignancy, metastatic bone disease, and bone marrow-based disorders such as multiple myeloma. Several bisphosphonates are now in clinical use for the management of osteoporosis, and others are currently in clinical development. This review will focus on the use of widely available bisphosphonates for the treatment of osteoporosis in postmenopausal women and men.

Mechanisms of action

Bisphosphonates preferentially bind to the surface of bone at sites of active remodeling and alter osteoclast activity. Recently, two distinct

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molecular mechanisms responsible for the effects of bisphosphonates on osteoclast function have been proposed [3]. Non-nitrogen-containing bisphosphonates (etidronate, clodronate, and tiludronate) alter cellular function by being metabolized to cytotoxic ATP-bisphosphonate analogues [4]. The more potent nitrogen-containing members of this drug class including alendronate, risedronate, ibandronate, and zoledronic acid, inhibit farnesyl pyrophosphatase and other distal steps in the intracellular mevalonate pathway [5–7]. As a consequence, the post-translational modification by prenylation of important intracellular regulatory proteins such as Ras and Rho is impaired, causing the inhibition of recruitment or differentiation of osteoclast precursors, the impairment of several intracellular enzymes and the induction of osteoclast apoptosis or cell death [1]. The result is a decrease in the rate at which new bone remodeling units are activated and a decrease in the amount of bone resorbing work each bone-remodeling unit performs. Indirectly and more slowly, osteoblast function and bone formation are decreased. A reduction in bone turnover occurs that can be applied clinically. Differences in the two side-chain structures determine both the potency, duration of action, side effects and possibly other clinical or skeletal parameters of the various bisphosphonate compounds.

Rationale for the use of bisphosphonates in treating osteoporosis

The goal of therapy in patients with or at risk for osteoporosis is to reduce the incidence of fractures by preserving or improving bone mass and bone quality. The bone loss that occurs after menopause in women and in older men and women is a consequence of increased and unbalanced bone remodeling such that osteoclastic bone resorption exceeds bone formation by osteoblasts. Remodeling sites serve as “stress risers” in thinned trabeculae [8], and high bone turnover is a risk factor for fracture independent of bone density in elderly subjects [9]. Normalizing bone turnover with bisphosphonates reduces the number of stress risers, restores the balance of bone remodeling and effectively prevents the progression of bone loss and deterioration of bone structure [10–12].

Skeletal effects of bisphosphonates

Up to 50% of the absorbed dose is quickly taken up by the skeleton. The remainder of the drug undergoes renal excretion without metabolism. Bisphosphonates have a long residual half-life (months to years) in skeletal tissue. The drug retained in the skeleton has relatively little effect because it is effectively isolated from osteoclasts when buried by newly formed bone.

Therapy with bisphosphonates suppresses biochemical indices of bone resorption very quickly with the reduction to about 50% of baseline at 1 month and to a stable nadir of 50% to 70% by 3 months [13,14]. Bone

formation falls more slowly, reaching a steady state after 6 to 12 months of treatment. Bone density increases modestly, most quickly during the first year of treatment. Values in the proximal femur plateau after about 2 years of treatment while bone mineral density (BMD) in the lumbar spine continues to increase at a slower rate (75% per year) for several years [15,16]. The initial increase in BMD is caused by the temporary dissociation between bone resorption and bone forming rates resulting in a closing of the so-called “remodeling space” [17,18]. The subsequent increase in bone density is caused by a progressive increase in the mineral density of bone tissue, a consequence of reduced bone turnover and increasing age of the bone tissue [19,20]. Bisphosphonate therapy preserves but does not restore bone volume or structure.

Clinically relevant reductions in the incidence of vertebral and non-vertebral fractures (including hip fractures) have been demonstrated with bisphosphonate therapy in patients at high risk for fracture [21] (Table 1). No effect on fracture rates has been observed in patients at low risk. The exact mechanism(s) by which fracture reduction is effected is uncertain [22]. In patients with osteoporosis, therapeutic effectiveness was not influenced by patients’ age or baseline BMD values. There is a statistically significant but modest correlation between the changes in BMD induced by treatment with anti-remodeling drugs and the subsequent reduction in fracture rates. In the alendronate studies, larger increases in BMD did not result in more effective fracture protection [23]. Estimates of the contribution of the change in BMD to vertebral fracture reduction with bisphosphonates have ranged from 17% to 28% [24]. No relationship between pre-treatment biochemical marker values and fracture reduction with treatment has been noted, but a significant correlation exists between the change in markers with therapy and fracture protection [25]. It is likely that the direct effect of bisphosphonates (the suppression of bone turnover) effects fracture risk by decreasing the number of bone remodeling sites, preserving bone structure and increasing bone density (Fig. 1). These observations have important implications for the evaluating and monitoring of the responses to bisphosphonate treatment.

Specific bisphosphonate drugs

Alendronate

Alendronate, the most extensively studied bisphosphonate, is administered in doses of 10 mg per day or 70 mg per week for treating women with osteoporosis and at doses of 5 mg per day or 35 mg per week for prevention of bone loss in lower risk patients. A dose-dependent increase in BMD and decrease in bone turnover was noted [13,26,27]. With 10 mg daily, bone density increased by 8.6% in the lumbar spine and 6.5% in the femoral neck after 2 years. Bone loss in the forearm was slowed but not prevented.

Table 1
Summary of pivotal clinical trials demonstrating effects of bisphosphonate therapy on spine or hip fracture risk in women with postmenopausal osteoporosis

Drug	Reference	No. of subjects	Average age (years)	Previous vertebral fractures (%)	Duration of study (years)	Fracture incidence (%)		Relative risk reduction (%)	CI
						Control group	Treatment group		
Vertebral fractures									
Alendronate	[70] ^a	994	64	20	3	6.2	3.2	48	(5,72)
	[13] ^b	2027	71	>96	2.8	15	8	47	(32,59)
	[29] ^b	4432	68	0	4.2	3	2	44	(20,61)
Risedronate	[49]	1628	69	80	3	16.3	11.3	41	(18,57)
	[92]	814	71	100	3	29	18.1	49	(27,64)
Etidronate	[109]	423	65	100	2	9.3	4.1	56	(not stated)
Hip fractures									
Alendronate	[13]	2027	71	>96	2.8	2.2	1.1	51	(1,77)
	[29] ^{c,d}	4432	68	0	4.2	2.2	1.2	56	(3,82)
	[29] ^{c,e}	4432	68	0	4.2	0.4	0.8	N/A	
Risedronate	[80] ^f	5455	74	38	3	3.2	1.9	40	(10,60)
	[80] ^g	1128	—	—	3	5.7	2.3	60	(20,80)
	[80] ^h	3886	83	44	3	5.1	4.2	20	(-20,40)

Direct comparisons between trials cannot be made because of differences in patient populations.

^a Pooled alendronate doses.

^b Alendronate 5 mg/day for 2 years, then 10 mg/day.

^c Post hoc analysis.

^d In subgroup with femoral neck BMD T-score ≤ -2.5 .

^e In subgroup with femoral neck BMD T-score > -2.5 .

^f In group with femoral neck BMD T-score ≤ -2.5 .

^g In group with femoral neck BMD T-score ≤ -2.5 and previous vertebral fractures.

^h In group with clinical risk factors for hip fracture. BMD status unknown.

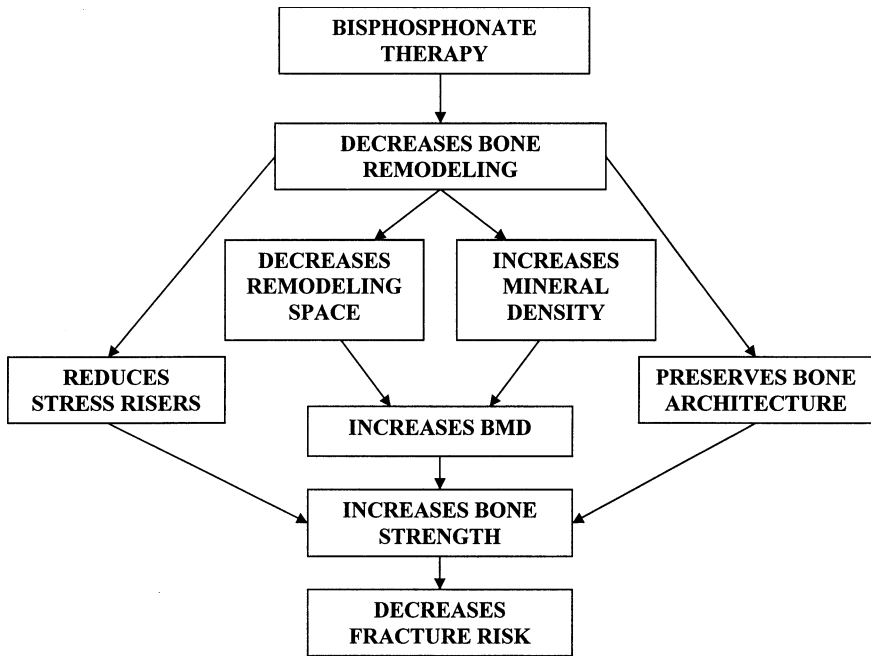


Fig. 1. Mechanisms by which bisphosphonate therapy reduces fracture risk. The primary effect is to reduce bone turnover resulting in multiple secondary effects that, in concert, increase bone strength and reduce the risk of fracture.

Markers of bone resorption were suppressed to the lower half of the normal premenopausal range. Administering the full week's dose of alendronate on a single day had the same effects on bone density and both the rate and pattern of bone turnover, as did standard daily dosing [28]. In a prospective study of 2027 women with pre-existing vertebral fractures, alendronate therapy for 3 years reduced the incidence of vertebral, hip and wrist fractures by about 50% [29]. In women without previous vertebral fractures but with low BMD, vertebral fracture incidence was reduced by 44% over 4 years [30]. In the sub-group of those women whose bone density T-score value was ≤ -2.5 , the incidence of clinical osteoporotic fractures decreased 36%. No effect on non-vertebral fracture was observed in women with T-score values > -2.5 [31]. In another study, therapy for 1 year significantly reduced the incidence of non-vertebral fractures in women with low bone density (T-score ≤ -2) [32]. A reduction in clinical apparent vertebral fractures was seen within the first year of treatment and, in a meta-analysis, protection from hip fracture was evident after 18 months of treatment [33]. Effects of therapy on bone density and turnover rates persisted with treatment for up to 7 years [16], but fracture rates could not be assessed adequately because of the absence of a placebo group after 3 years.

An alendronate dose of 5 mg daily for 4 years protected young postmenopausal women from bone loss, but no effect on fracture rate was observed in this low risk population [34,35]. In men with low BMD (T-score < -2) treated with 10 mg daily for 2 years, bone density in the spine and hip increased and vertebral fracture rates decreased [36]. The effect was similar in men with and without androgen deficiency. Treatment of men and women receiving glucocorticoids with 5 or 10 mg daily preserved bone density and, after 2 years, reduced the incidence of new vertebral fractures [37].

Risedronate

Risedronate is administered in a dose of 5 mg daily or 35 mg once weekly for the prevention and treatment of postmenopausal and glucocorticoid-induced osteoporosis. In early postmenopausal women (40 to 60 years of age) with normal bone mass, treatment with 5 mg daily for 2 years normalized bone turnover and produced BMD increases of 5.7% in the lumbar spine and 5.4% in the hip compared with placebo [14]. Similar findings were observed in women with low bone mass [38]. The non-inferiority of a 35 mg weekly dose with standard daily dosing was demonstrated in women with osteoporosis [39]. In randomized placebo-controlled trials in women with osteoporosis and prevalent vertebral fractures, treatment with 5 mg risedronate daily for 3 years reduced the incidence of new vertebral fractures (41% to 49%) and decreased the risk of non-vertebral fractures by 33% to 39% [40,41]. Radiographic vertebral fractures were reduced by 61% to 65% during the first year of therapy, and multiple vertebral deformities were reduced by 77% to 96% during that interval. The salutary effect on vertebral fracture risk continued for at least 5 years. Treatment for 3 years decreased the incidence of hip fracture by 40% in elderly women known to have osteoporosis, but no effect risk was observed in older women enrolled in the study because of fall-related risk factors [42]. Treatment of patients just beginning or remaining on long-term glucocorticoid therapy preserved or increased bone density and decreased vertebral fracture incidence by 70% during the first year of therapy [43].

Etidronate

Etidronate was the first bisphosphonate evaluated for the treatment of osteoporosis. The drug is approved for this indication in Canada but not in the United States. It is administered in a cyclic intermittent regimen of 400 mg daily for 2 weeks, repeated every 3 months. Continuous dosing resulted in impaired mineralization of new bone. Prospective randomized trials demonstrated that etidronate increased spine bone density and decreased the incidence of new vertebral fractures, especially in high-risk patients [44–46]. A meta-analysis suggested that etidronate therapy in postmenopausal women with osteoporosis increased BMD by 4.1% in the lumbar spine and by 2.3% in the femoral neck relative to control groups and reduced vertebral

fracture risk by 37% [47]. Appropriate prospective studies demonstrating protection from non-vertebral fracture or hip fracture have not been performed. Etidronate also prevented bone loss in young postmenopausal women [48] and in men and women receiving glucocorticoid therapy [49].

Other bisphosphonates

Pamidronate, administered intravenously, is approved for the treatment of Paget's disease and hypercalcemia of malignancy. Treatment with the original oral formulation of pamidronate increased BMD and reduced vertebral fracture risk in women with osteoporosis [50]. Because the oral form of this drug evaluated in North America was associated with a high incidence of esophageal complications [51], pamidronate is no longer being developed for osteoporosis treatment. Intravenous dosing with 30 mg every 2 to 3 months transiently suppressed bone turnover and increased bone density in the spine, but confirmation of fracture protection with this regimen is lacking [52].

Ibandronate is a potent aminobisphosphonate currently in clinical development for osteoporosis management. Oral treatment with 2.5 mg daily or an intermittent regimen of 20 mg given every other day for 13 doses and repeated every 3 months increased BMD in the spine and total hip and reduced vertebral fracture incidence [53,54]. Short intravenous injection of ibandronate in doses up to 2 mg given every 3 months increased BMD in the lumbar spine [55]. Indices of bone turnover were quickly suppressed but returned toward baseline before the next dose. A statistically insignificant reduction in new vertebral fractures occurred with this regimen, possibly because the dose studied was too small [56].

Zoledronic acid is a very potent aminobisphosphonate currently approved as an intravenous treatment for hypercalcemia of malignancy and is now in clinical development as a treatment for osteoporosis management [57]. Treatment with 4 mg zoledronic acid per year given by short intravenous infusion in quarterly, semi-annual or annual doses increased bone density in the lumbar spine and proximal femur in women with osteoporosis [58]. Bone turnover was suppressed for at least 12 months after a single 4-mg dose. How long suppression lasts after a single dose is not yet known. Side effects resembling acute phase reaction were reported in a small number of subjects.

It is unlikely that the new, more potent bisphosphonates will be more clinically effective than our current agents. The objective of anti-remodeling therapy is to normalize bone turnover, and this is accomplished by alendronate and risedronate. Extreme suppression of bone turnover has not been documented to provide more fracture protection and theoretically could be harmful. The new drugs will provide alternate dosing regimens and different tolerability profiles and will allow more treatment options for patients with special needs. While it is appealing to consider the use of intravenous pamidronate and zoledronic acid in patients intolerant of oral

aminobisphosphonates, the routine use of these agents cannot be advised until more is known about the anti-fracture effects, their safety and the duration of the suppression of bone turnover.

Dosing

All bisphosphonates are very poorly absorbed from the gastrointestinal tract and avidly adhere to food, other medications (especially calcium salts or supplements) and even to simple beverages like coffee. Taking bisphosphonates with or after meals limits bioavailability. The absorption of alendronate decreased by 40% to 50% when taken 30 to 60 minutes before a meal compared with its fractional absorption of 0.7% when taken after an overnight fast and two hours before a meal [59]. Absorption was also impaired when taken within two hours following a meal. Similar data were reported for other bisphosphonate drugs [60]. For these reasons, bisphosphonates should be taken on an empty stomach with four to eight ounces of plain water, and other food, beverages or medication should be avoided for at least 30 minutes. To minimize reflux and possible gastrointestinal (GI) symptoms, the patient should not lie down for at least 30 minutes after dosing.

Tolerability and side effects

The overall clinical experience demonstrates that bisphosphonates are very well tolerated when dosed and administered appropriately.

Gastrointestinal effects

Gastrointestinal symptoms are the most frequent side effects attributed to bisphosphonate use. Nitrogen-containing bisphosphonates (especially alendronate) have been associated with esophageal irritation and ulceration, resulting in heartburn, substernal chest pain and nausea [61–64]. These symptoms usually occur within the first few weeks of therapy. Rare cases of significant gastrointestinal bleeding and esophageal perforation or stricture have been reported [65]. With both alendronate and risedronate, upper GI side effects were observed with similar frequency (from 20% to 40%) of older women with osteoporosis in both the placebo and active treatment groups [66,67]. In clinical practice, upper GI symptoms occur in 20% to 30% of women receiving alendronate. The high background of upper GI symptoms among older adults complicates the interpretation of these complaints in patients receiving bisphosphonates. It is often difficult to correlate symptoms to the drug, and they may be related to concomitant medications including calcium supplements. Recurrence of symptoms is uncommon when patients are either rechallenged with alendronate or switched to risedronate [44,68]. Whether there is a difference in the clinical tolerability of risedronate and alendronate is unknown.

The mechanism of the esophageal irritation seems to require both direct exposure of the esophageal mucosa to the drug and an acid environment caused by esophageal reflux. Proper dosing minimizes the frequency of this problem. There is a perception among clinicians that weekly dosing with alendronate or risedronate is better tolerated than is daily dosing, although no differences in the frequency of gastrointestinal side effects were observed between daily and weekly dosing groups in clinical trials [26,39]. The effectiveness of H₂-blockers or proton pump inhibitors in minimizing symptoms in patients receiving bisphosphonate therapy has not been evaluated. In clinical trials, concomitant use with NSAID drugs did not increase the GI symptoms or complications associated with those agents. An increased frequency of small gastric ulcers has been reported with alendronate therapy in some endoscopy studies, but the clinical relevance of these findings is not known [69]. Bisphosphonates should be discontinued in patients who experience significant or persistent worsening of upper GI symptoms. Patients with esophageal motility disorders and stricture or who are unable to remain upright after dosing are not good candidates for therapy with alendronate and perhaps other oral nitrogen-containing bisphosphonates. Nausea and diarrhea, usually mild, are infrequent side effects in patients receiving etidronate therapy, and this drug can often be used in patients who experience upper GI intolerance to nitrogen-containing bisphosphonates.

Skeletal effects

Because these agents accumulate in the skeleton, concerns exist about the effects of long-term or high dose bisphosphonate therapy. Continuous long-term administration of etidronate resulted in bone pain, fractures and histological evidence of osteoid accumulation that resembled osteomalacia [11], and impaired fracture healing has been observed with high dose therapy in animals [70]. Neither the effect on bone mineralization or impaired fracture healing has been seen in humans with cyclic intermittent etidronate therapy or with other more potent bisphosphonates at doses used clinically. Unexplained transient bone pain was infrequently observed soon after beginning alendronate therapy in clinical trials.

The major clinical concern with potent bisphosphonates is the potential impairment of bone quality by over-suppressing normal skeletal repair mechanisms or causing excess aging and mineralization of the bone tissue. High doses of alendronate impair healing of microdamage in animals [71], an effect that is difficult to evaluate in the clinical setting. Biochemical markers of bone turnover fall to the middle or lower portion of the normal premenopausal range with bisphosphonate therapy in humans, are stable with continued use, and may remain suppressed upon withdrawal of alendronate or zoledronic acid. The microscopic appearance of bone in bisphosphonate-treated subjects is normal, but histomorphometric indices of bone turnover are suppressed by more than 90% with alendronate

therapy [72]. However, treatment for up to 5 years with risedronate and 7 years with etidronate or alendronate has not been associated with clinical evidence of skeletal harm [16], and skeletal complications have not been reported with high-dose pamidronate therapy for malignant disease [52].

Alterations in mineral metabolism

By acutely suppressing bone resorption, bisphosphonate therapy caused a physiologically significant reduction in serum calcium concentration. In clinical trials, as many as 20% of patients experienced a fall in serum calcium levels to below the normal reference range [13]. The nadir of this effect occurred within the first month of therapy and was associated with an appropriate elevation of serum parathyroid hormone levels. Both calcium and PTH values returned to near baseline levels with continued use. The fall in serum calcium was not associated with symptoms, but the patients in these trials were calcium and vitamin D replete. Clinically evident hypocalcemia has been observed with bisphosphonate therapy in patients with vitamin D deficiency or osteomalacia [12,73–75]. Bisphosphonates should not be administered to patients with hypocalcemia or whose intakes of calcium or vitamin D are inadequate until those problems have been corrected. High dose etidronate therapy has been associated with mild hyperphosphatemia [76].

Acute phase reaction

Intravenous or high-dose oral therapy with nitrogen-containing bisphosphonates was associated with an acute phase reaction manifested by fever, myalgias and lymphopenia lasting a few days [77]. This generally occurred with the initial but not subsequent exposure to the drug.

Other effects

Inflammation of ocular structures (iritis, uveitis, and conjunctivitis), dermatological conditions, allergic manifestations, and abnormal tests of liver and renal function have been reported in patients receiving bisphosphonates [72,78–85]. Other than the renal failure that can occur following high-dose intravenous bisphosphonate therapy, the symptoms and findings were generally mild and abated when therapy was discontinued.

Special clinical circumstances

Elderly patients

No clinical trial has evaluated the anti-fracture efficacy of bisphosphonates in women with osteoporosis over age 80. Changes in bone density similar to those demonstrated in younger postmenopausal women were

observed with alendronate treatment of older women (ages 65 to 85) [86] and those in long-term care facilities (ages 70 to 90) [87]. Bone density changes were also observed with risedronate in women over age 80 [42]. Both alendronate and risedronate were well tolerated in these older women. Because fracture protection is evident within the first few months of beginning therapy, it seems reasonable to consider bisphosphonate therapy in elderly patients with osteoporosis.

Premenopausal women

Fortunately there are few indications for bisphosphonate use in premenopausal women, with high-dose glucocorticoid therapy being a possible exception. In estrogen-replete premenopausal women with idiopathic osteoporosis, bone turnover is usually not elevated, and the effectiveness of anti-remodeling treatment in this setting has not been studied. Bisphosphonate use has not been evaluated during pregnancy. In animal studies, very high dose therapy with bisphosphonates caused fetal skeletal deformities and fetal wastage because of maternal hypocalcemia. If therapy were clinically justified, minimal risk to subsequent pregnancy should be expected because of the small doses used to treat osteoporosis and because serum levels quickly fall to very low levels when therapy is stopped.

Children with osteoporosis

A small series of children with juvenile osteoporosis treated with bisphosphonates have been reported with apparent clinical benefit [88,89]. In children with osteogenesis imperfecta treated with intermittent intravenous pamidronate, significant increases in bone density and reduction of fracture incidence were reported without impairment of skeletal growth [90,91]. No studies have yet evaluated the effect of bisphosphonate treatment in children receiving glucocorticoid therapy.

Non-white patients

The major clinical trials with bisphosphonates have evaluated treatment efficacy almost exclusively in white subjects. Bone density and bone turnover marker responses similar to the data from whites have been reported in African-American [92] and Asian populations [93–95].

Renal insufficiency

Bisphosphonate therapy has not been evaluated in patients with significant renal impairment. Skeletal metabolism in patients with renal failure is complex. Bisphosphonates would not be indicated in patients with osteomalacia and would likely not be effective in those with the adynamic form of the renal osteodystrophy [96]. Hypocalcemia would be a risk

associated with treating patients with marked secondary hyperparathyroidism. For these reasons, no clear justification for bisphosphonate therapy in patients with renal failure or on dialysis exists. Bisphosphonates are partially dialyzable [97]. An adjustment in dose frequency might be warranted for patients with osteoporosis who have moderate renal insufficiency (GFR 10–30 mL/L).

Organ transplant

Rapid bone loss and vertebral fractures occur following organ transplantation caused by the skeletal effects of the immunosuppressive regimen. Bisphosphonate therapy retards bone loss after transplantation and is now being used routinely in many transplant centers [98,99].

Immobilized patients

Disuse osteoporosis is characterized by increased bone resorption, most marked during the early stages of physical inactivity. This suggests that bisphosphonate therapy should be effective. Treatment prevents disuse bone loss in animals and reduces the hypercalcemia associated with bed rest in humans [100–102]. This effect may have applicability in patients who are non-ambulatory because of neurological or other medical problems and in the protection of the skeleton during interplanetary space flight.

Combining bisphosphonates with other treatments for osteoporosis

Small additional increments in BMD occurred when bisphosphonates were combined with estrogen or raloxifene [103–107], but the effects of these agents are not additive or synergistic. Once bone turnover is normalized by one anti-remodeling drug, there is little left for an additional agent to accomplish. Whether the small effects observed provide additional fracture protection is unproven. Biochemical and histomorphometric indices of bone turnover were more suppressed when anti-remodeling agents are combined, but whether this promotes or harms bone health is unknown. Except in special circumstances or when non-response to a single agent has been documented, the use of anti-remodeling agents in combination is not recommended. The availability of anabolic agents will provide the opportunity for true combination therapy. Bone turnover markers increased (as expected) when women who were already receiving alendronate were treated with parathyroid hormone 1-34 [108]. Bone density increased substantially when women were treated with alendronate following parathyroid hormone 1-84 therapy [109]. More experience and information about simultaneous or sequential use of bisphosphonates with anabolic agents is needed.

Monitoring response to bisphosphonate therapy

It is now customary to assess the response to bisphosphonate therapy by repeating the BMD measurement at 1 or 2 years. Because the average increase in BMD in the spine (5% to 8%) only modestly exceeds the smallest change between two measurements that can be detected in individual subjects (3% to 4%), many patients will appear to have no appreciable increase in bone density with treatment. No apparent response is seen in the proximal femur in most patients. Not observing a response is not indicative of treatment failure and does not warrant a change in treatment. It is reassuring to observe a significant reduction in the level of a biochemical marker of bone turnover at 3 to 6 months after treatment is begun. However, because of the high precision error of marker assays, not observing a decrease is not necessarily evidence of non-response. In those few patients who appear to lose bone density or whose turnover markers do not clearly fall, a review of whether and how they take the drug and a search for medical or metabolic factors that impair response (including vitamin D deficiency) are appropriate. Until more effective treatments are available, rarely is it necessary or justified to substitute or add another osteoporosis drug.

How long should therapy be continued?

The duration of therapy is dictated by the effectiveness of continued treatment and by what occurs when the drug is stopped. No waning of effect has been demonstrated with continuous bisphosphonate use for at least 7 years. Within the first year of stopping alendronate or risedronate after 2 years of treatment in early postmenopausal women, indices of bone turnover returned toward baseline, and bone loss resumed at a rate similar to the control group [35,53,60]. In contrast, discontinuing alendronate therapy in older women who were treated for 2 to 5 years resulted in stable BMD and persistent suppression of bone turnover for at least 2 years [16,110]. This raises the possibility of limiting alendronate therapy to 5 years, at least in relatively low risk patients, and resuming treatment when markers of bone turnover increase again [111]. Because substantial variability in the binding avidity to mineral crystal exists among the bisphosphonate compounds, there may be differences among these drugs in the duration of effect upon discontinuation.

Summary

Bisphosphonates now occupy a prominent position among therapeutic options for the prevention and treatment of various forms of osteoporosis. Their clinical profile of bone-specific efficacy, rapid response, protection from both spine and hip fractures in patients with osteoporosis, and excellent tolerability is all that can be expected of an anti-remodeling

drug. Even in the era of anabolic agents, bisphosphonates will continue to be important treatment options.

It is not possible to compare or contrast the clinical effectiveness of the various bisphosphonates on the basis of existing data. Despite marked differences in the *in vitro* potency of drugs, the clinical responses to each of the bisphosphonates discussed above are similar. New bisphosphonates may not be more effective but will provide different tolerability profiles and different routes of administration, thereby increasing the number of patients in whom bisphosphonates can be used. Having these effective agents challenges clinicians to identify the most appropriate patients for bisphosphonate use and to develop strategies to improve acceptance of and adherence to these useful agents.

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